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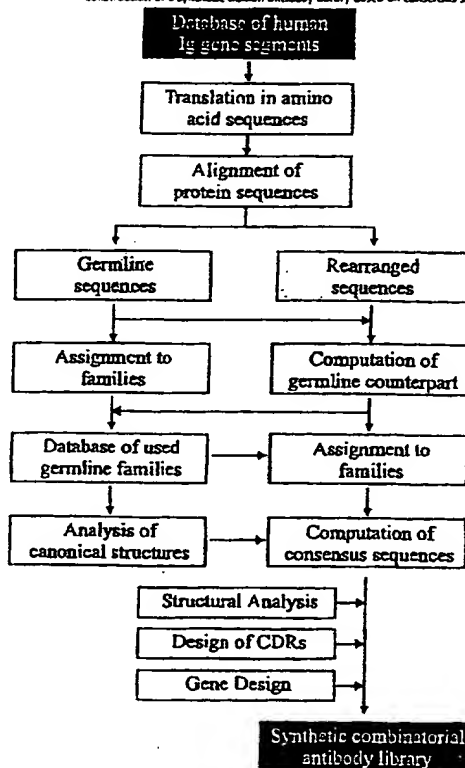
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(54) Title: PROTEIN/(POLY)PEPTIDE LIBRARIES

(57) Abstract

The present invention relates to synthetic DNA sequences which encode one or more collections of homologous proteins/(poly)peptides, and methods for generating and applying libraries of these DNA sequences. In particular, the invention relates to the preparation of a library of human-derived antibody genes by the use of synthetic consensus sequences which cover the structural repertoire of antibodies encoded in the human genome. Furthermore, the invention relates to the use of a single consensus antibody gene as a universal framework for highly diverse antibody libraries.

construction of a synthetic human antibody library based on consensus sequences



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## Protein/(Poly)peptide Libraries

### Field of the Invention

The present invention relates to synthetic DNA sequences which encode one or more collections of homologous proteins/(poly)peptides, and methods for generating and applying libraries of these DNA sequences. In particular, the invention relates to the preparation of a library of human-derived antibody genes by the use of synthetic consensus sequences which cover the structural repertoire of antibodies encoded in the human genome. Furthermore, the invention relates to the use of a single consensus antibody gene as a universal framework for highly diverse antibody libraries.

### Background to the Invention

All current recombinant methods which use libraries of proteins/(poly)peptides, e.g. antibodies, to screen for members with desired properties, e.g. binding a given ligand, do not provide the possibility to improve the desired properties of the members in an easy and rapid manner. Usually a library is created either by inserting a random oligonucleotide sequence into one or more DNA sequences cloned from an organism, or a family of DNA sequences is cloned and used as the library. The library is then screened, e.g. using phage display, for members which show the desired property. The sequences of one or more of these resulting molecules are then determined. There is no general procedure available to improve these molecules further on.

Winter (EP 0 368 684 B1) has provided a method for amplifying (by PCR), cloning, and expressing antibody variable region genes. Starting with these genes he was able to create libraries of functional antibody fragments by randomizing the CDR3 of the heavy and/or the light chain. This process is functionally equivalent to the natural process of VJ and VDJ recombination which occurs during the development of B-cells in the immune system.

However the Winter invention does not provide a method for optimizing the binding affinities of antibody fragments further on, a process which would be functionally equivalent to the naturally occurring phenomenon of "affinity maturation", which is provided by the present invention. Furthermore, the Winter invention does not provide for artificial variable region genes, which represent a whole family of

structurally similar natural genes, and which can be assembled from synthetic DNA oligonucleotides. Additionally, Winter does not enable the combinatorial assembly of portions of antibody variable regions, a feature which is provided by the present invention. Furthermore, this approach has the disadvantage that the genes of all antibodies obtained in the screening procedure have to be completely sequenced, since, except for the PCR priming regions, no additional sequence information about the library members is available. This is time and labor intensive and potentially leads to sequencing errors.

The teaching of Winter as well as other approaches have tried to create large antibody libraries having high diversity in the complementarity determining regions (CDRs) as well as in the frameworks to be able to find antibodies against as many different antigens as possible. It has been suggested that a single universal framework may be useful to build antibody libraries, but no approach has yet been successful.

Another problem lies in the production of reagents derived from antibodies. Small antibody fragments show exciting promise for use as therapeutic agents, diagnostic reagents, and for biochemical research. Thus, they are needed in large amounts, and the expression of antibody fragments, e.g. Fv, single-chain Fv (scFv), or Fab in the periplasm of *E. coli* (Skerra & Plückthun, 1988; Better et al., 1988) is now used routinely in many laboratories. Expression yields vary widely, however. While some fragments yield up to several mg of functional, soluble protein per liter and OD of culture broth in shake flask culture (Carter et al., 1992, Plückthun et al. 1996), other fragments may almost exclusively lead to insoluble material, often found in so-called inclusion bodies. Functional protein may be obtained from the latter in modest yields by a laborious and time-consuming refolding process. The factors influencing antibody expression levels are still only poorly understood. Folding efficiency and stability of the antibody fragments, protease lability and toxicity of the expressed proteins to the host cells often severely limit actual production levels, and several attempts have been tried to increase expression yields. For example, Knappik & Plückthun (1995) could show that expression yield depends on the antibody sequence. They identified key residues in the antibody framework which influence expression yields dramatically. Similarly, Ullrich et al. (1995) found that point mutations in the CDRs can increase the yields in periplasmic antibody fragment expression. Nevertheless, these strategies are only applicable to a few antibodies. Since the Winter invention uses existing repertoires of antibodies, no influence on expressibility of the genes is possible.



Furthermore, the findings of Knappik & Plückthun and Ullrich demonstrate that the knowledge about antibodies, especially about folding and expression is still increasing. The Winter invention does not allow to incorporate such improvements into the library design.

The expressibility of the genes is important for the library quality as well, since the screening procedure relies in most cases on the display of the gene product on a phage surface, and efficient display relies on at least moderate expression of the gene.

These disadvantages of the existing methodologies are overcome by the present invention, which is applicable for all collections of homologous proteins. It has the following novel and useful features illustrated in the following by antibodies as an example:

Artificial antibodies and fragments thereof can be constructed based on known antibody sequences, which reflect the structural properties of a whole group of homologous antibody genes. Therefore it is possible to reduce the number of different genes without any loss in the structural repertoire. This approach leads to a limited set of artificial genes, which can be synthesized de novo, thereby allowing introduction of cleavage sites and removing unwanted cleavage sites. Furthermore, this approach enables (i), adapting the codon usage of the genes to that of highly expressed genes in any desired host cell and (ii), analyzing all possible pairs of antibody light (L) and heavy (H) chains in terms of interaction preference, antigen preference or recombinant expression titer, which is virtually impossible using the complete collection of antibody genes of an organism and all combinations thereof.

The use of a limited set of completely synthetic genes makes it possible to create cleavage sites at the boundaries of encoded structural sub-elements. Therefore, each gene is built up from modules which represent structural sub-elements on the protein/(poly)peptide level. In the case of antibodies, the modules consist of "framework" and "CDR" modules. By creating separate framework and CDR modules, different combinatorial assembly possibilities are enabled. Moreover, if two or more artificial genes carry identical pairs of cleavage sites at the boundaries of each of the genetic sub-elements, pre-built libraries of sub-elements can be inserted in these genes simultaneously, without any additional information related to any particular gene sequence. This strategy enables rapid optimization of, for example, antibody affinity, since DNA cassettes encoding libraries of genetic sub-elements can be (i), pre-built, stored and reused and (ii), inserted in any of these

sequences at the right position without knowing the actual sequence or having to determine the sequence of the individual library member.

Additionally, new information about amino acid residues important for binding, stability, or solubility and expression could be integrated into the library design by replacing existing modules with modules modified according to the new observations.

The limited number of consensus sequences used for creating the library allows to speed up the identification of binding antibodies after screening. After having identified the underlying consensus gene sequence, which could be done by sequencing or by using fingerprint restriction sites, just those part(s) comprising the random sequence(s) have to be determined. This reduces the probability of sequencing errors and of false-positive results.

The above mentioned cleavage sites can be used only if they are unique in the vector system where the artificial genes have been inserted. As a result, the vector has to be modified to contain none of these cleavage sites. The construction of a vector consisting of basic elements like resistance gene and origin of replication, where cleavage sites have been removed, is of general interest for many cloning attempts. Additionally, these vector(s) could be part of a kit comprising the above mentioned artificial genes and pre-built libraries.

The collection of artificial genes can be used for a rapid humanization procedure of non-human antibodies, preferably of rodent antibodies. First, the amino acid sequence of the non-human, preferably rodent antibody is compared with the amino acid sequences encoded by the collection of artificial genes to determine the most homologous light and heavy framework regions. These genes are then used for insertion of the genetic sub-elements encoding the CDRs of the non-human, preferably rodent antibody.

Surprisingly, it has been found that with a combination of only one consensus sequence for each of the light and heavy chains of a scFv fragment an antibody repertoire could be created yielding antibodies against virtually every antigen. Therefore, one aspect of the present invention is the use of a single consensus sequence as a universal framework for the creation of useful (poly)peptide libraries and antibody consensus sequences useful therefor.

## Detailed Description of the Invention

The present invention enables the creation of useful libraries of (poly)peptides. In a first embodiment, the invention provides for a method of setting up nucleic acid sequences suitable for the creation of said libraries. In a first step, a collection of at least three homologous proteins is identified and then analyzed. Therefore, a database of the protein sequences is established where the protein sequences are aligned to each other. The database is used to define subgroups of protein sequences which show a high degree of similarity in both the sequence and, if information is available, in the structural arrangement. For each of the subgroups a (poly)peptide sequence comprising at least one consensus sequence is deduced which represents the members of this subgroup; the complete collection of (poly)peptide sequences represent therefore the complete structural repertoire of the collection of homologous proteins. These artificial (poly)peptide sequences are then analyzed, if possible, according to their structural properties to identify unfavorable interactions between amino acids within said (poly)peptide sequences or between said or other (poly)peptide sequences, for example, in multimeric proteins. Such interactions are then removed by changing the consensus sequence accordingly. The (poly)peptide sequences are then analyzed to identify sub-elements such as domains, loops, helices or CDRs. The amino acid sequence is backtranslated into a corresponding coding nucleic acid sequence which is adapted to the codon usage of the host planned for expressing said nucleic acid sequences. A set of cleavage sites is set up in a way that each of the sub-sequences encoding the sub-elements identified as described above, is flanked by two sites which do not occur a second time within the nucleic acid sequence. This can be achieved by either identifying a cleavage site already flanking a sub-sequence or by changing one or more nucleotides to create the cleavage site, and by removing that site from the remaining part of the gene. The cleavage sites should be common to all corresponding sub-elements or sub-sequences, thus creating a fully modular arrangement of the sub-sequences in the nucleic acid sequence and of the sub-elements in the corresponding (poly)peptide.

In a further embodiment, the invention provides for a method which sets up two or more sets of (poly)peptides, where for each set the method as described above is performed, and where the cleavage sites are not only unique within each set but also between any two sets. This method can be applied for the creation of (poly)peptide libraries comprising for example two  $\alpha$ -helical domains from two different proteins, where said library is screened for novel hetero-association domains.

In yet a further embodiment, at least two of the sets as described above, are derived from the same collection of proteins or at least a part of it. This describes libraries comprising for example, but not limited to, two domains from antibodies such as VH and VL, or two extracellular loops of transmembrane receptors.

In another embodiment, the nucleic acid sequences set up as described above, are synthesized. This can be achieved by any one of several methods well known to the practitioner skilled in the art, for example, by total gene synthesis or by PCR-based approaches.

In one embodiment, the nucleic acid sequences are cloned into a vector. The vector could be a sequencing vector, an expression vector or a display (e.g. phage display) vector, which are well known to those skilled in the art. Any vector could comprise one nucleic acid sequence, or two or more nucleic sequences, either in different or the same operon. In the last case, they could either be cloned separately or as contiguous sequences.

In one embodiment, the removal of unfavorable interactions as described above, leads to enhanced expression of the modified (poly)peptides.

In a preferred embodiment, one or more sub-sequences of the nucleic acid sequences are replaced by different sequences. This can be achieved by excising the sub-sequences using the conditions suitable for cleaving the cleavage sites adjacent to or at the end of the sub-sequence, for example, by using a restriction enzyme at the corresponding restriction site under the conditions well known to those skilled in the art, and replacing the sub-sequence by a different sequence compatible with the cleaved nucleic acid sequence. In a further preferred embodiment, the different sequences replacing the initial sub-sequence(s) are genomic or rearranged genomic sequences, for example in grafting CDRs from non-human antibodies onto consensus antibody sequences for rapid humanization of non-human antibodies. In the most preferred embodiment, the different sequences are random sequences, thus replacing the sub-sequence by a collection of sequences to introduce variability and to create a library. The random sequences can be assembled in various ways, for example by using a mixture of mononucleotides or preferably a mixture of trinucleotides (Virnekås et al., 1994) during automated oligonucleotide synthesis, by error-prone PCR or by other methods well known to the practitioner in the art. The random sequences may be completely randomized or biased towards or against certain codons according to

the amino acid distribution at certain positions in known protein sequences. Additionally, the collection of random sub-sequences may comprise different numbers of codons, giving rise to a collection of sub-elements having different lengths.

In another embodiment, the invention provides for the expression of the nucleic acid sequences from a suitable vector and under suitable conditions well known to those skilled in the art.

In a further preferred embodiment, the (poly)peptides expressed from said nucleic acid sequences are screened and, optionally, optimized. Screening may be performed by using one of the methods well known to the practitioner in the art, such as phage-display, selectively infective phage, polysome technology to screen for binding, assay systems for enzymatic activity or protein stability. (Poly)peptides having the desired property can be identified by sequencing of the corresponding nucleic acid sequence or by amino acid sequencing or mass spectrometry. In the case of subsequent optimization, the nucleic acid sequences encoding the initially selected (poly)peptides can optionally be used without sequencing. Optimization is performed by repeating the replacement of sub-sequences by different sequences, preferably by random sequences, and the screening step one or more times.

The desired property the (poly)peptides are screened for is preferably, but not exclusively, selected from the group of optimized affinity or specificity for a target molecule, optimized enzymatic activity, optimized expression yields, optimized stability and optimized solubility.

In one embodiment, the cleavage sites flanking the sub-sequences are sites recognized and cleaved by restriction enzymes, with recognition and cleavage sequences being either identical or different, the restricted sites either having blunt or sticky ends.

The length of the sub-elements is preferably, but not exclusively ranging between 1 amino acid, such as one residue in the active site of an enzyme or a structure-determining residue, and 150 amino acids, as for whole protein domains. Most preferably, the length ranges between 3 and 25 amino acids, such as most commonly found in CDR loops of antibodies.

The nucleic acid sequences could be RNA or, preferably, DNA.

In one embodiment, the (poly)peptides have an amino acid pattern characteristic of a particular species. This can for example be achieved by deducing the consensus sequences from a collection of homologous proteins of just one species, most preferably from a collection of human proteins. Since the (poly)peptides comprising consensus sequences are artificial, they have to be compared to the protein sequence(s) having the closest similarity to ensure the presence of said characteristic amino acid pattern.

In one embodiment, the invention provides for the creation of libraries of (poly)peptides comprising at least part of members or derivatives of the immunoglobulin superfamily, preferably of member or derivatives of the immunoglobulins. Most preferably, the invention provides for the creation of libraries of human antibodies, wherein said (poly)peptides are or are derived from heavy or light chain variable regions wherein said structural sub-elements are framework regions (FR) 1, 2, 3, or 4 or complementary determining regions (CDR) 1, 2, or 3. In a first step, a database of published antibody sequences of human origin is established where the antibody sequences are aligned to each other. The database is used to define subgroups of antibody sequences which show a high degree of similarity in both the sequence and the canonical fold of CDR loops (as determined by analysis of antibody structures). For each of the subgroups a consensus sequence is deduced which represents the members of this subgroup; the complete collection of consensus sequences represent therefore the complete structural repertoire of human antibodies.

These artificial genes are then constructed e.g. by total gene synthesis or by the use of synthetic genetic subunits. These genetic subunits correspond to structural sub-elements on the (poly)peptide level. On the DNA level, these genetic subunits are defined by cleavage sites at the start and the end of each of the sub-elements, which are unique in the vector system. All genes which are members of the collection of consensus sequences are constructed such that they contain a similar pattern of corresponding genetic sub-sequences. Most preferably, said (poly)peptides are or are derived from the HuCAL consensus genes: V $\kappa$ 1, V $\kappa$ 2, V $\kappa$ 3, V $\kappa$ 4, V $\lambda$ 1, V $\lambda$ 2, V $\lambda$ 3, VH1A, VH1B, VH2, VH3, VH4, VH5, VH6, C $\kappa$ , C $\lambda$ , CH1 or any combination of said HuCAL consensus genes.

This collection of DNA molecules can then be used to create libraries of antibodies or antibody fragments, preferably Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragments, which may be used as sources of specificities against new target antigens. Moreover, the affinity of the antibodies can be optimized using pre-built library cassettes and a general procedure. The invention provides a method for identifying one or more genes encoding one or more antibody fragments which

binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule. Preferably, an scFv fragment library comprising the combination of HuCAL VH3 and HuCAL V $\lambda$ 2 consensus genes and at least a random sub-sequence encoding the heavy chain CDR3 sub-element is screened for binding antibodies. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated.

Particularly preferred is a method in which one or more of the genetic subunits (e.g. the CDRs) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are selected, collected and used as starting material for the next library. Here, one or more of the remaining genetic subunits are randomized as described above.

A further embodiment of the present invention relates to fusion proteins by providing for a DNA sequence which encodes both the (poly)peptide, as described above, as well as an additional moiety. Particularly preferred are moieties which have a useful therapeutic function. For example, the additional moiety may be a toxin molecule which is able to kill cells (Vitetta et al., 1993). There are numerous examples of such toxins, well known to the one skilled in the art, such as the bacterial toxins *Pseudomonas* exotoxin A, and diphtheria toxin, as well as the plant toxins ricin, abrin, modeccin, saporin, and gelonin. By fusing such a toxin for example to an antibody fragment, the toxin can be targeted to, for example, diseased cells, and thereby have a beneficial therapeutic effect. Alternatively, the additional moiety may be a cytokine, such as IL-2 (Rosenberg & Lotze, 1986), which has a particular effect (in this case a T-cell proliferative effect) on a family of cells. In a further embodiment, the additional moiety may confer on its (poly)peptide partner a means of detection and/or purification. For example, the fusion protein could comprise the modified antibody fragment and an enzyme commonly used for detection purposes, such as alkaline phosphatase (Blake et al., 1984). There are numerous other moieties which can be used as detection or purification tags, which are well known to the practitioner skilled in the art. Particularly preferred are peptides comprising at least five histidine residues (Hochuli et al., 1988), which are able to bind to metal ions,

and can therefore be used for the purification of the protein to which they are fused (Lindner et al., 1992). Also provided for by the invention are additional moieties such as the commonly used C-myc and FLAG tags (Hopp et al., 1988; Knappik & Plückthun, 1994).

By engineering one or more fused additional domains, antibody fragments or any other (poly)peptide can be assembled into larger molecules which also fall under the scope of the present invention. For example, mini-antibodies (Pack, 1994) are dimers comprising two antibody fragments, each fused to a self-associating dimerization domain. Dimerization domains which are particularly preferred include those derived from a leucine zipper (Pack & Plückthun, 1992) or helix-turn-helix motif (Pack et al., 1993).

All of the above embodiments of the present invention can be effected using standard techniques of molecular biology known to anyone skilled in the art.

In a further embodiment, the random collection of sub-sequences (the library) is inserted into a singular nucleic acid sequence encoding one (poly)peptide, thus creating a (poly)peptide library based on one universal framework. Preferably a random collection of CDR sub-sequences is inserted into a universal antibody framework, for example into the HuCAL H3k2 single-chain Fv fragment described above.

In further embodiments, the invention provides for nucleic acid sequence(s), vector(s) containing the nucleic acid sequence(s), host cell(s) containing the vector(s), and (poly)peptides, obtainable according to the methods described above.

In a further preferred embodiment, the invention provides for modular vector systems being compatible with the modular nucleic acid sequences encoding the (poly)peptides. The modules of the vectors are flanked by restriction sites unique within the vector system and essentially unique with respect to the restriction sites incorporated into the nucleic acid sequences encoding the (poly)peptides, except for example the restriction sites necessary for cloning the nucleic acid sequences into the vector. The list of vector modules comprises origins of single-stranded replication, origins of double-stranded replication for high- and low copy number plasmids, promotor/operator, repressor or terminator elements, resistance genes, potential recombination sites, gene III for display on filamentous phages, signal sequences, purification and detection tags, and sequences of additional moieties.



The vectors are preferably, but not exclusively, expression vectors or vectors suitable for expression and screening of libraries.

In another embodiment, the invention provides for a kit, comprising one or more of the list of nucleic acid sequence(s), recombinant vector(s), (poly)peptide(s), and vector(s) according to the methods described above, and suitable host cell(s) for producing the (poly)peptide(s).

In a preferred embodiment, the invention provides for the creation of libraries of human antibodies. In a first step, a database of published antibody sequences of human origin is established. The database is used to define subgroups of antibody sequences which show a high degree of similarity in both the sequence and the canonical fold (as determined by analysis of antibody structures). For each of the subgroups a consensus sequence is deduced which represents the members of this subgroup; the complete collection of consensus sequences represent therefore the complete structural repertoire of human antibodies.

These artificial genes are then constructed by the use of synthetic genetic subunits. These genetic subunits correspond to structural sub-elements on the protein level. On the DNA level, these genetic subunits are defined by cleavage sites at the start and the end of each of the subelements, which are unique in the vector system. All genes which are members of the collection of consensus sequences are constructed such that they contain a similar pattern of said genetic subunits.

This collection of DNA molecules can then be used to create libraries of antibodies which may be used as sources of specificities against new target antigens. Moreover, the affinity of the antibodies can be optimised using pre-built library cassettes and a general procedure. The invention provides a method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated.

Particularly preferred is a method in which one or more of the genetic subunits (e.g. the CDR's) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are eluted, collected and used as starting material for the next library. Here, one or more of the remaining genetic subunits are randomised as described above.

## Definitions

### Protein:

The term protein comprises monomeric polypeptide chains as well as homo- or heteromultimeric complexes of two or more polypeptide chains connected either by covalent interactions (such as disulphide bonds) or by non-covalent interactions (such as hydrophobic or electrostatic interactions).

### Analysis of homologous proteins:

The amino acid sequences of three or more proteins are aligned to each other (allowing for introduction of gaps) in a way which maximizes the correspondence between identical or similar amino acid residues at all positions. These aligned sequences are termed homologous if the percentage of the sum of identical and/or similar residues exceeds a defined threshold. This threshold is commonly regarded by those skilled in the art as being exceeded when at least 15% of the amino acids in the aligned genes are identical, and at least 30% are similar. Examples for families of homologous proteins are: immunoglobulin superfamily, scavenger receptor superfamily, fibronectin superfamilies (e.g. type II and III), complement control protein superfamily, cytokine receptor superfamily, cystine knot proteins, tyrosine kinases, and numerous other examples well known to one of ordinary skill in the art.

### Consensus sequence:

Using a matrix of at least three aligned amino acid sequences, and allowing for gaps in the alignment, it is possible to determine the most frequent amino acid residue at each position. The consensus sequence is that sequence which comprises the amino acids which are most frequently represented at each position. In the event that two or more amino acids are equally represented at a single position, the consensus sequence includes both or all of those amino acids.

### Removing unfavorable interactions:

The consensus sequence is per se in most cases artificial and has to be analyzed in order to change amino acid residues which, for example, would prevent the resulting molecule to adapt a functional tertiary structure or which would block the interaction with other (poly)peptide chains in multimeric complexes. This can be done either by (i) building a three-dimensional model of the consensus sequence using known related structures as a template, and identifying amino acid residues within the model which may interact unfavorably with each other, or (ii) analyzing the matrix of aligned amino acid sequences in order to detect combinations of amino

acid residues within the sequences which frequently occur together in one sequence and are therefore likely to interact with each other. These probable interaction-pairs are then tabulated and the consensus is compared with these "interaction maps". Missing or wrong interactions in the consensus are repaired accordingly by introducing appropriate changes in amino acids which minimize unfavorable interactions.

Identification of structural sub-elements:

Structural sub-elements are stretches of amino acid residues within a protein/(poly)peptide which correspond to a defined structural or functional part of the molecule. These can be loops (e.g. CDR loops of an antibody) or any other secondary or functional structure within the protein/(poly)peptide (domains,  $\alpha$ -helices,  $\beta$ -sheets, framework regions of antibodies, etc.). A structural sub-element can be identified using known structures of similar or homologous (poly)peptides, or by using the above mentioned matrices of aligned amino acid sequences. Here the variability at each position is the basis for determining stretches of amino acid residues which belong to a structural sub-element (e.g. hypervariable regions of an antibody).

Sub-sequence:

A sub-sequence is defined as a genetic module which is flanked by unique cleavage sites and encodes at least one structural sub-element. It is not necessarily identical to a structural sub-element.

Cleavage site:

A short DNA sequence which is used as a specific target for a reagent which cleaves DNA in a sequence-specific manner (e.g. restriction endonucleases).

Compatible cleavage sites:

Cleavage sites are compatible with each other, if they can be efficiently ligated without modification and, preferably, also without adding an adapter molecule..

Unique cleavage sites:

A cleavage site is defined as unique if it occurs only once in a vector containing at least one of the genes of interest, or if a vector containing at least one of the genes of interest could be treated in a way that only one of the cleavage sites could be used by the cleaving agent.

Corresponding (poly)peptide sequences:

Sequences deduced from the same part of one group of homologous proteins are called corresponding (poly)peptide sequences.

Common cleavage sites:

A cleavage site in at least two corresponding sequences, which occurs at the same functional position (i.e. which flanks a defined sub-sequence), which can be hydrolyzed by the same cleavage tool and which yields identical compatible ends is termed a common cleavage site.

Excising genetic sub-sequences:

A method which uses the unique cleavage sites and the corresponding cleavage reagents to cleave the target DNA at the specified positions in order to isolate, remove or replace the genetic sub-sequence flanked by these unique cleavage sites.

Exchanging genetic sub-sequences:

A method by which an existing sub-sequence is removed using the flanking cleavage sites of this sub-sequence, and a new sub-sequence or a collection of sub-sequences, which contain ends compatible with the cleavage sites thus created, is inserted.

Expression of genes:

The term expression refers to in vivo or in vitro processes, by which the information of a gene is transcribed into mRNA and then translated into a protein/(poly)peptide. Thus, the term expression refers to a process which occurs inside cells, by which the information of a gene is transcribed into mRNA and then into a protein. The term expression also includes all events of post-translational modification and transport, which are necessary for the (poly)peptide to be functional.

Screening of protein/(poly)peptide libraries:

Any method which allows isolation of one or more proteins/(poly)peptides having a desired property from other proteins/(poly)peptides within a library.

Amino acid pattern characteristic for a species:

A (poly)peptide sequence is assumed to exhibit an amino acid pattern characteristic for a species if it is deduced from a collection of homologous proteins from just this species.

Immunoglobulin superfamily (IgSF):

The IgSF is a family of proteins comprising domains being characterized by the immunoglobulin fold. The IgSF comprises for example T-cell receptors and the immunoglobulins (antibodies).

Antibody framework:

A framework of an antibody variable domain is defined by Kabat et al. (1991) as the part of the variable domain which serves as a scaffold for the antigen binding loops of this variable domain.

Antibody CDR:

The CDRs (complementarity determining regions) of an antibody consist of the antigen binding loops, as defined by Kabat et al. (1991). Each of the two variable domains of an antibody Fv fragment contain three CDRs.

HuCAL:

Acronym for Human Combinatorial Antibody Library. Antibody Library based on modular consensus genes according to the invention (see Example 1).

Antibody fragment:

Any portion of an antibody which has a particular function, e.g. binding of antigen. Usually, antibody fragments are smaller than whole antibodies. Examples are Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragments. Additionally, antibody fragments are often engineered to include new functions or properties.

Universal framework:

One single framework which can be used to create the full variability of functions, specificities or properties which is originally sustained by a large collection of different frameworks, is called universal framework.

Binding of an antibody to its target:

The process which leads to a tight and specific association between an antibody and a corresponding molecule or ligand is called binding. A molecule or ligand or any part of a molecule or ligand which is recognized by an antibody is called the target.

Replacing genetic sub-sequences

A method by which an existing sub-sequence is removed using the flanking cleavage sites of this sub-sequence, and a new sub-sequence or collection of sub-

sequences, which contains ends compatible with the cleavage sites thus created, is inserted.

Assembling of genetic sequences:

Any process which is used to combine synthetic or natural genetic sequences in a specific manner in order to get longer genetic sequences which contain at least parts of the used synthetic or natural genetic sequences.

Analysis of homologous genes:

The corresponding amino acid sequences of two or more genes are aligned to each other in a way which maximizes the correspondence between identical or similar amino acid residues at all positions. These aligned sequences are termed homologous if the percentage of the sum of identical and/or similar residues exceeds a defined threshold. This threshold is commonly regarded by those skilled in the art as being exceeded when at least 15 per cent of the amino acids in the aligned genes are identical, and at least 30 per cent are similar.

***Legends to Figures and Tables***

- Fig. 1:** Flow chart outlining the process of construction of a synthetic human antibody library based on consensus sequences.
- Fig. 2:** Alignment of consensus sequences designed for each subgroup (amino acid residues are shown with their standard one-letter abbreviation). (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. The positions are numbered according to Kabat (1991). In order to maximize homology in the alignment, gaps (—) have been introduced in the sequence at certain positions.
- Fig. 3:** Gene sequences of the synthetic V kappa consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.
- Fig. 4:** Gene sequences of the synthetic V lambda consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.
- Fig. 5:** Gene sequences of the synthetic V heavy chain consensus genes. The corresponding amino acid sequences (see Fig. 2) as well as the unique cleavage sites are also shown.
- Fig. 6:** Oligonucleotides used for construction of the consensus genes. The oligos are named according to the corresponding consensus gene, e.g. the gene V $\kappa$ 1 was constructed using the six oligonucleotides O1K1 to O1K6. The oligonucleotides used for synthesizing the genes encoding the constant domains C $\kappa$  (OCLK1 to 8) and CH1 (OCH1 to 8) are also shown.
- Fig. 7A/B:** Sequences of the synthetic genes encoding the constant domains C $\kappa$  (A) and CH1 (B). The corresponding amino acid sequences as well as unique cleavage sites introduced in these genes are also shown.
- Fig. 7C:** Functional map and sequence of module M24 comprising the synthetic C $\lambda$  gene segment (huCL lambda).
- Fig. 7D:** Oligonucleotides used for synthesis of module M24.
- Fig. 8:** Sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-V $\kappa$ 2. The signal sequence (amino acids 1 to 21) was derived from the *E. coli* phoA gene (Skerra &



Plückthun, 1988). Between the *phoA* signal sequence and the VH3 domain, a short sequence stretch encoding 4 amino acid residues (amino acid 22 to 25) has been inserted in order to allow detection of the single-chain fragment in Western blot or ELISA using the monoclonal antibody M1 (Knappik & Plückthun, 1994). The last 6 basepairs of the sequence were introduced for cloning purposes (EcoRI site).

**Fig. 9:** Plasmid map of the vector pLG10.3 used for phage display of the H3 $\kappa$ 2 scFv fragment. The vector is derived from pLG10 and contains the gene for the lac operon repressor, *lacI*, the artificial operon encoding the H3 $\kappa$ 2-gene3ss fusion under control of the lac promoter, the *lpp* terminator of transcription, the single-strand replication origin of the *E. coli* phage f1 (F1\_ORI), a gene encoding  $\beta$ -lactamase (*bla*) and the ColEI derived origin of replication.

**Fig. 10:** Sequencing results of independent clones from the initial library, translated into the corresponding amino acid sequences. (A) Amino acid sequence of the VH3 consensus heavy chain CDR3 (position 93 to 102, Kabat numbering). (B) Amino acid sequences of 12 clones of the 10-mer library. (C) Amino acid sequences of 11 clones of the 15-mer library, \*: single base deletion.

**Fig. 11:** Expression test of individual library members. (A) Expression of 9 independent clones of the 10-mer library. (B) Expression of 9 independent clones of the 15-mer library. The lane designated with M contains the size marker. Both the gp3-scFv fusion and the scFv monomer are indicated.

**Fig. 12:** Enrichment of specific phage antibodies during the panning against FITC-BSA. The initial as well as the subsequent fluorescein-specific sub-libraries were panned against the blocking buffer and the ratio of the phage eluted from the FITC-BSA coated well vs. that from the powder milk coated well from each panning round is presented as the „specificity factor“.

**Fig. 13:** Phage ELISA of 24 independent clones after the third round of panning tested for binding on FITC-BSA.

**Fig. 14:** Competition ELISA of selected FITC-BSA binding clones. The ELISA signals ( $OD_{405nm}$ ) of scFv binding without inhibition are taken as 100%.

**Fig. 15:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against FITC-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).

- Fig. 16:** Coomassie-Blue stained SDS-PAGE of the purified anti-fluorescein scFv fragments: M: molecular weight marker, A: total soluble cell extract after induction, B: fraction of the flow-through, C, D and E: purified scFv fragments 1HA-3E4, 1HA-3E5 and 1HA-3E10, respectively.
- Fig. 17:** Enrichment of specific phage antibodies during the panning against  $\beta$ -estradiol-BSA, testosterone-BSA, BSA, ESL-1, interleukin-2, lymphotoxin- $\beta$ , and LeY-BSA after three rounds of panning.
- Fig. 18:** ELISA of selected ESL-1 and  $\beta$ -estradiol binding clones
- Fig. 19:** Selectivity and cross-reactivity of HuCAL antibodies: in the diagonal specific binding of HuCAL antibodies can be seen, off-diagonal signals show non-specific cross-reactivity.
- Fig. 20:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against  $\beta$ -estradiol-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). One clone is derived from the 10mer library.
- Fig. 21:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against testosterone-BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).
- Fig. 22:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against lymphotoxin- $\beta$ , translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). One clone comprises a 14mer CDR, presumably introduced by incomplete coupling of the trinucleotide mixture during oligonucleotide synthesis.
- Fig. 23:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against ESL-1, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering). Two clones are derived from the 10mer library. One clone comprises a 16mer CDR, presumably introduced by chain elongation during oligonucleotide synthesis using trinucleotides.
- Fig. 24:** Sequencing results of the heavy chain CDR3s of independent clones after 3 rounds of panning against BSA, translated into the corresponding amino acid sequences (position 93 to 102, Kabat numbering).
- Fig. 25:** Schematic representation of the modular pCAL vector system.
- Fig. 25a:** List of restriction sites already used in or suitable for the modular HuCAL genes and pCAL vector system.
- Fig. 26:** List of the modular vector elements for the pCAL vector series: shown are only those restriction sites which are part of the modular system.

- Fig. 27: Functional map and sequence of the multi-cloning site module (MCS)
- Fig. 28: Functional map and sequence of the pMCS cloning vector series.
- Fig. 29: Functional map and sequence of the pCAL module M1 (see Fig. 26).
- Fig. 30: Functional map and sequence of the pCAL module M7-III (see Fig. 26).
- Fig. 31: Functional map and sequence of the pCAL module M9-II (see Fig. 26).
- Fig. 32: Functional map and sequence of the pCAL module M11-II (see Fig. 26).
- Fig. 33: Functional map and sequence of the pCAL module M14-Ext2 (see Fig. 26).
- Fig. 34: Functional map and sequence of the pCAL module M17 (see Fig. 26).
- Fig. 35: Functional map and sequence of the modular vector pCAL4.
- Fig. 35a: Functional maps and sequences of additional pCAL modules (M2, M3, M7I, M7II, M8, M10II, M11II, M12, M13, M19, M20, M21, M41) and of low-copy number plasmid vectors (pCALO1 to pCALO3).
- Fig. 35b: List of oligonucleotides and primers used for synthesis of pCAL vector modules.
- Fig. 36: Functional map and sequence of the  $\beta$ -lactamase cassette for replacement of CDRs for CDR library cloning.
- Fig. 37: Oligo and primer design for V $\kappa$  CDR3 libraries
- Fig. 38: Oligo and primer design for V $\lambda$  CDR3 libraries
- Fig. 39: Functional map of the pBS13 expression vector series.
- Fig. 40: Expression of all 49 HuCAL scFvs obtained by combining each of the 7 VH genes with each of the 7 VL genes (pBS13, 30°C): Values are given for the percentage of soluble vs. insoluble material, the total and the soluble amount compared to the combination H3 $\kappa$ 2, which was set to 100%. In addition, the corresponding values for the McPC603 scFv are given.

**Table 1:** Summary of human immunoglobulin germline sequences used for computing the germline membership of rearranged sequences. (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. (1) The germline name used in the various calculations, (2) the references number for the corresponding sequence (see appendix for sequence related citations), (3) the family where each sequence belongs to and (4), the various names found in literature for germline genes with identical amino acid sequences.

**Table 2:** Rearranged human sequences used for the calculation of consensus sequences. (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. The table summarized the name of the sequence (1),

the length of the sequence in amino acids (2), the germline family (3) as well as the computed germline counterpart (4). The number of amino acid exchanges between the rearranged sequence and the germline sequence is tabulated in (5), and the percentage of different amino acids is given in (6). Column (7) gives the references number for the corresponding sequence (see appendix for sequence related citations).

**Table 3:** Assignment of rearranged V sequences to their germline counterparts. (A) kappa sequences, (B) lambda sequences and (C), heavy chain sequences. The germline genes are tabulated according to their family (1), and the number of rearranged genes found for every germline gene is given in (2).

**Table 4:** Computation of the consensus sequence of the rearranged V kappa sequences. (A), V kappa subgroup 1, (B), V kappa subgroup 2, (C), V kappa subgroup 3 and (D), V kappa subgroup 4. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. (1) Amino acids are given with their standard one-letter abbreviations (and B means D or N, Z means E or Q and X means any amino acid). The statistical analysis summarizes the number of sequences found at each position (2), the number of occurrences of the most common amino acid (3), the amino acid residue which is most common at this position (4), the relative frequency of the occurrence of the most common amino acid (5) and the number of different amino acids found at each position (6).

**Table 5:** Computation of the consensus sequence of the rearranged V lambda sequences. (A), V lambda subgroup 1, (B), V lambda subgroup 2, and (C), V lambda subgroup 3. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. Abbreviations are the same as in Table 4.

**Table 6:** Computation of the consensus sequence of the rearranged V heavy chain sequences. (A), V heavy chain subgroup 1A, (B), V heavy chain subgroup 1B, (C), V heavy chain subgroup 2, (D), V heavy chain subgroup 3, (E), V heavy chain subgroup 4, (F), V heavy chain subgroup 5, and (G), V heavy chain subgroup 6. The number of each amino acid found at each position is tabulated together with the statistical analysis of the data. Abbreviations are the same as in Table 4.

## Examples

### Example 1: Design of a Synthetic Human Combinatorial Antibody Library (HuCAL)

The following example describes the design of a fully synthetic human combinatorial antibody library (HuCAL), based on consensus sequences of the human immunoglobulin repertoire, and the synthesis of the consensus genes. The general procedure is outlined in Fig. 1.

#### 1.1 Sequence database

##### 1.1.1 Collection and alignment of human immunoglobulin sequences

In a first step, sequences of variable domains of human immunoglobulins have been collected and divided into three sub bases: V heavy chain (VH), V kappa (V $\kappa$ ) and V lambda (V $\lambda$ ). For each sequence, the gene sequence was then translated into the corresponding amino acid sequence. Subsequently, all amino acid sequences were aligned according to Kabat et al. (1991). In the case of V $\lambda$  sequences, the numbering system of Chuchana et al. (1990) was used. Each of the three main databases was then divided into two further sub bases: the first sub base contained all sequences derived from rearranged V genes, where more than 70 positions of the sequence were known. The second sub base contained all germline gene segments (without the D- and J- minigenes; pseudogenes with internal stop codons were also removed). In all cases, where germline sequences with identical amino acid sequence but different names were found, only one sequence was used (see Table 1). The final databases of rearranged sequences contained 386, 149 and 674 entries for V $\kappa$ , V $\lambda$  and VH, respectively. The final databases of germline sequences contained 48, 26 and 141 entries for V $\kappa$ , V $\lambda$  and VH, respectively.

##### 1.1.2 Assignment of sequences to subgroups

The sequences in the three germline databases were then grouped according to sequence homology (see also Tomlinson et al., 1992, Williams & Winter, 1993, and Cox et al., 1994). In the case of V $\kappa$ , 7 families could be established. V $\lambda$  was divided into 8 families and VH into 6 families. The VH germline genes of the VH7 family (Van Dijk et al., 1993) were grouped into the VH1 family, since the genes of the two families are highly homologous. Each family contained different numbers of germline genes, varying from 1 (for example VH6) to 47 (VH3).

## 1.2 Analysis of sequences

### 1.2.1 Computation of germline membership

For each of the 1209 amino acid sequences in the databases of rearranged genes, the nearest germline counterpart, i.e. the germline sequence with the smallest number of amino acid differences was then calculated. After the germline counterpart was found, the number of somatic mutations which occurred in the rearranged gene and which led to amino acid exchanges could be tabulated. In 140 cases, the germline counterpart could not be calculated exactly, because more than one germline gene was found with an identical number of amino acid exchanges. These rearranged sequences were removed from the database. In a few cases, the number of amino acid exchanges was found to be unusually large (>20 for VL and >25 for VH), indicating either heavily mutated rearranged genes or derivation from germline genes not present in the database. Since it was not possible to distinguish between these two possibilities, these sequences were also removed from the database. Finally, 12 rearranged sequences were removed from the database because they were found to have very unusual CDR lengths and composition or unusual amino acids at canonical positions (see below). In summary, 1023 rearranged sequences out of 1209 (85%) could be clearly assigned to their germline counterparts (see Table 2).

After this calculation, every rearranged gene could be arranged in one of the families established for the germline genes. Now the usage of each germline gene, i.e. the number of rearranged genes which originate from each germline gene, could be calculated (see Table 2). It was found that the usage was strongly biased towards a subset of germline genes, whereas most of the germline genes were not present as rearranged genes in the database and therefore apparently not used in the immune system (Table 3). This observation had already been reported in the case of V $\kappa$  (Cox, et al., 1994). All germline gene families, where no or only very few rearranged counterparts could be assigned, were removed from the database, leaving 4 V $\kappa$ , 3 V $\lambda$ , and 6 VH families.

### 1.2.2 Analysis of CDR conformations

The conformation of the antigen binding loops of antibody molecules, the CDRs, is strongly dependent on both the length of the CDRs and the amino acid residues located at the so-called canonical positions (Chothia & Lesk, 1987). It has been found that only a few canonical structures exist, which determine the structural

repertoire of the immunoglobulin variable domains (Chothia et al., 1989). The canonical amino acid positions can be found in CDR as well as framework regions. The 13 used germline families defined above (7 VL and 6 VH) were now analyzed for their canonical structures in order to define the structural repertoire encoded in these families.

In 3 of the 4 V $\kappa$  families (V $\kappa$ 1, 2 and 4), one different type of CDR1 conformation could be defined for every family. The family V $\kappa$ 3 showed two types of CDR1 conformation: one type which was identical to V $\kappa$ 1 and one type only found in V $\kappa$ 3. All V $\kappa$  CDR2s used the same type of canonical structure. The CDR3 conformation is not encoded in the germline gene segments. Therefore, the 4 V $\kappa$  families defined by sequence homology and usage corresponded also to 4 types of canonical structures found in V $\kappa$  germline genes.

The 3 V $\lambda$  families defined above showed 3 types of CDR1 conformation, each family with one unique type. The V $\lambda$ 1 family contained 2 different CDR1 lengths (13 and 14 amino acids), but identical canonical residues, and it is thought that both lengths adopt the same canonical conformation (Chothia & Lesk, 1987). In the CDR2 of the used V $\lambda$  germlines, only one canonical conformation exists, and the CDR3 conformation is not encoded in the germline gene segments. Therefore, the 3 V $\lambda$  families defined by sequence homology and usage corresponded also to 3 types of canonical structures.

The structural repertoire of the human VH sequences was analyzed in detail by Chothia et al., 1992. In total, 3 conformations of CDR1 (H1-1, H1-2 and H1-3) and 6 conformations of CDR2 (H2-1, H2-2, H2-3, H2-4, H2-5 and H2-x) could be defined. Since the CDR3 is encoded in the D- and J-minigene segments, no particular canonical residues are defined for this CDR.

All the members of the VH1 family defined above contained the CDR1 conformation H1-1, but differed in their CDR2 conformation: the H2-2 conformation was found in 6 germline genes, whereas the conformation H2-3 was found in 8 germline genes. Since the two types of CDR2 conformations are defined by different types of amino acid at the framework position 72, the VH1 family was divided into two subfamilies: VH1A with CDR2 conformation H2-2 and VH1B with the conformation H2-3. The members of the VH2 family all had the conformations H1-3 and H2-1 in CDR1 and CDR2, respectively. The CDR1 conformation of the VH3 members was found in all cases to be H1-1, but 4 different types were found in CDR2 (H2-1, H2-3, H2-4 and H2-x). In these CDR2 conformations, the canonical framework residue 71 is always

defined by an arginine. Therefore, it was not necessary to divide the VH3 family into subfamilies, since the 4 types of CDR2 conformations were defined solely by the CDR2 itself. The same was true for the VH4 family. Here, all 3 types of CDR1 conformations were found, but since the CDR1 conformation was defined by the CDR itself (the canonical framework residue 26 was found to be glycine in all cases), no subdivisions were necessary. The CDR2 conformation of the VH4 members was found to be H2-1 in all cases. All members of the VH5 family were found to have the conformation H1-1 and H2-2, respectively. The single germline gene of the VH6 family had the conformations H1-3 and H2-5 in CDR1 and CDR2, respectively.

In summary, all possible CDR conformations of the V $\kappa$  and V $\lambda$  genes were present in the 7 families defined by sequence comparison. From the 12 different CDR conformations found in the used VH germline genes, 7 could be covered by dividing the family VH1 into two subfamilies, thereby creating 7 VH families. The remaining 5 CDR conformations (3 in the VH3 and 2 in the VH4 family) were defined by the CDRs themselves and could be created during the construction of CDR libraries. Therefore, the structural repertoire of the used human V genes could be covered by 49 (7 x 7) different frameworks.

### 1.2.3 Computation of consensus sequences

The 14 databases of rearranged sequences (4 V $\kappa$ , 3 V $\lambda$  and 7 VH) were used to compute the HuCAL consensus sequences of each subgroup (4 HuCAL- V $\kappa$ , 3 HuCAL- V $\lambda$ , 7 HuCAL- VH, see Table 4, 5 and 6). This was done by counting the number of amino acid residues used at each position (position variability) and subsequently identifying the amino acid residue most frequently used at each position. By using the rearranged sequences instead of the used germline sequences for the calculation of the consensus, the consensus was weighted according to the frequency of usage. Additionally, frequently mutated and highly conserved positions could be identified. The consensus sequences were cross-checked with the consensus of the germline families to see whether the rearranged sequences were biased at certain positions towards amino acid residues which do not occur in the collected germline sequences, but this was found not to be the case. Subsequently, the number of differences of each of the 14 consensus sequences to each of the germline sequences found in each specific family was calculated. The overall deviation from the most homologous germline sequence was found to be 2.4 amino acid residues (s.d. = 2.7), ensuring that the "artificial" consensus sequences



can still be considered as truly human sequences as far as immunogenicity is concerned.

### 1.3 Structural analysis

So far, only sequence information was used to design the consensus sequences. Since it was possible that during the calculation certain artificial combinations of amino acid residues have been created, which are located far away in the sequence but have contacts to each other in the three dimensional structure, leading to destabilized or even misfolded frameworks, the 14 consensus sequences were analyzed according to their structural properties.

It was rationalized that all rearranged sequences present in the database correspond to functional and therefore correctly folded antibody molecules. Hence, the most homologous rearranged sequence was calculated for each consensus sequence. The positions where the consensus differed from the rearranged sequence were identified as potential "artificial residues" and inspected.

The inspection itself was done in two directions. First, the local sequence stretch around each potentially "artificial residue" was compared with the corresponding stretch of all the rearranged sequences. If this stretch was found to be truly artificial, i.e. never occurred in any of the rearranged sequences, the critical residue was converted into the second most common amino acid found at this position and analyzed again. Second, the potentially "artificial residues" were analyzed for their long range interactions. This was done by collecting all available structures of human antibody variable domains from the corresponding PDB files and calculating for every structure the number and type of interactions each amino acid residue established to each side-chain. These "interaction maps" were used to analyze the probable side-chain/side-chain interactions of the potentially "artificial residues". As a result of this analysis, the following residues were exchanged (given is the name of the gene, the position according to Kabat's numbering scheme, the amino acid found at this position as the most abundant one and the amino acid which was used instead):

VH2: S<sub>65</sub>T

Vκ1: N<sub>34</sub>A,

Vκ3: G<sub>9</sub>A, D<sub>60</sub>A, R<sub>77</sub>S

Vλ3: V<sub>78</sub>T

#### 1.4 Design of CDR sequences

The process described above provided the complete consensus sequences derived solely from the databases of rearranged sequences. It was rationalized that the CDR1 and CDR2 regions should be taken from the databases of used germline sequences, since the CDRs of rearranged and mutated sequences are biased towards their particular antigens. Moreover, the germline CDR sequences are known to allow binding to a variety of antigens in the primary immune response, where only CDR3 is varied. Therefore, the consensus CDRs obtained from the calculations described above were replaced by germline CDRs in the case of VH and V $\kappa$ . In the case of V $\lambda$ , a few amino acid exchanges were introduced in some of the chosen germline CDRs in order to avoid possible protease cleavage sites as well as possible structural constraints.

The CDRs of following germline genes have been chosen:

| <u>HuCAL gene</u>   | <u>CDR1</u>           | <u>CDR2</u>                                   |
|---------------------|-----------------------|---|
| HuCAL-VH1A          | VH1-12-1              | VH1-12-1                                      |
| HuCAL-VH1B          | VH1-13-16             | VH1-13-6,-7,-8,-9                             |
| HuCAL-VH2           | VH2-31-10,-11,-12,-13 | VH2-31-3,-4                                   |
| HuCAL-VH3           | VH3-13-8,-9,-10       | VH3-13-8,-9,-10                               |
| HuCAL-VH4           | VH4-11-7 to -14       | VH4-11-8,-9,-11,-12,-14,-16                   |
|                     |                       | VH4-31-17,-18,-19,-20                         |
| HuCAL-VH5           | VH5-12-1,-2           | VH5-12-1,-2                                   |
| HuCAL-VH6           | VH6-35-1              | VH6-35-1                                      |
| HuCAL-V $\kappa$ 1  | V $\kappa$ 1-14,-15   | V $\kappa$ 1-2,-3,-4,-5,-7,-8,-12,-13,-18,-19 |
| HuCAL-V $\kappa$ 2  | V $\kappa$ 2-6        | V $\kappa$ 2-6                                |
| HuCAL-V $\kappa$ 3  | V $\kappa$ 3-1,-4     | V $\kappa$ 3-4                                |
| HuCAL-V $\kappa$ 4  | V $\kappa$ 4-1        | V $\kappa$ 4-1                                |
| HuCAL-V $\lambda$ 1 | HUMLV117,DPL5         | DPL5  |
| HuCAL-V $\lambda$ 2 | DPL11,DPL12           | DPL12   |
| HuCAL-V $\lambda$ 3 | DPL23                 | HUMLV318                                      |

In the case of the CDR3s, any sequence could be chosen since these CDRs were planned to be the first to be replaced by oligonucleotide libraries. In order to study the expression and folding behavior of the consensus sequences in *E. coli*, it would be useful to have all sequences with the same CDR3, since the influence of the CDR3s on the folding behavior would then be identical in all cases. The dummy sequences QQHYTTPP and ARWGGDGFYAMDY were selected for the VL chains (kappa and lambda) and for the VH chains, respectively. These sequences are known to be compatible with antibody folding in *E. coli* (Carter et al., 1992).

### 1.5 Gene design

The final outcome of the process described above was a collection of 14 HuCAL amino acid sequences, which represent the frequently used structural antibody repertoire of the human immune system (see Figure 2). These sequences were back-translated into DNA sequences. In a first step, the back-translation was done using only codons which are known to be frequently used in *E. coli*. These gene sequences were then used for creating a database of all possible restriction endonuclease sites, which could be introduced without changing the corresponding amino acid sequences. Using this database, cleavage sites were selected which were located at the flanking regions of all sub-elements of the genes (CDRs and framework regions) and which could be introduced in all HuCAL VH, V $\kappa$  or V $\lambda$  genes simultaneously at the same position. In a few cases it was not possible to find cleavage sites for all genes of a subgroup. When this happened, the amino acid sequence was changed, if this was possible according to the available sequence and structural information. This exchange was then analyzed again as described above. In total, the following 6 amino acid residues were exchanged during this design (given is the name of the gene, the position according to Kabat's numbering scheme, the amino acid found at this position as the most abundant one and the amino acid which was used instead):

VH2: T<sub>3</sub>Q

VH6: S<sub>42</sub>G

V $\kappa$ 3: E<sub>1</sub>D, I<sub>58</sub>V

V $\kappa$ 4: K<sub>24</sub>R

V $\lambda$ 3: T<sub>22</sub>S

In one case (5'-end of VH framework 3) it was not possible to identify a single cleavage site for all 7 VH genes. Two different type of cleavage sites were used instead: BstEII for HuCAL VH1A, VH1B, VH4 and VH5, and NspV for HuCAL VH2, VH3, VH4 and VH6.

Several restriction endonuclease sites were identified, which were not located at the flanking regions of the sub-elements but which could be introduced in every gene of a given group without changing the amino acid sequence. These cleavage sites were also introduced in order to make the system more flexible for further improvements. Finally, all but one remaining restriction endonuclease sites were removed in every gene sequence. The single cleavage site, which was not removed was different in all genes of a subgroup and could be therefore used as a "fingerprint" site to ease the identification of the different genes by restriction digest. The designed genes, together with the corresponding amino acid sequences and the group-specific restriction endonuclease sites are shown in Figure 3, 4 and 5, respectively.

### ***1.6 Gene synthesis and cloning***

The consensus genes were synthesized using the method described by Prodromou & Pearl, 1992, using the oligonucleotides shown in Fig. 6. Gene segments encoding the human constant domains C $\kappa$ , C $\lambda$  and CH1 were also synthesized, based on sequence information given by Kabat et al., 1991 (see Fig. 6 and Fig. 7). Since for both the CDR3 and the framework 4 gene segments identical sequences were chosen in all HuCAL V $\kappa$ , V $\lambda$  and VH genes, respectively, this part was constructed only once, together with the corresponding gene segments encoding the constant domains. The PCR products were cloned into pCR-Script KS(+) (Stratagene, Inc.) or pZER0-1 (Invitrogen, Inc.) and verified by sequencing.

### **Example 2: Cloning and Testing of a HuCAL-Based Antibody Library**

A combination of two of the synthetic consensus genes was chosen after construction to test whether binding antibody fragments can be isolated from a library based on these two consensus frameworks. The two genes were cloned as a single-chain Fv (scFv) fragment, and a VH-CDR3 library was inserted. In order to test the library for the presence of functional antibody molecules, a selection procedure

was carried out using the small hapten fluorescein bound to BSA (FITC-BSA) as antigen.

### ***2.1 Cloning of the HuCAL VH3-Vk2 scFv fragment***

In order to test the design of the consensus genes, one randomly chosen combination of synthetic light and heavy gene (HuCAL-Vk2 and HuCAL-VH3) was used for the construction of a single-chain antibody (scFv) fragment. Briefly, the gene segments encoding the VH3 consensus gene and the CH1 gene segment including the CDR3 - framework 4 region, as well as the Vk2 consensus gene and the Cκ gene segment including the CDR3 - framework 4 region were assembled yielding the gene for the VH3-CH1 Fd fragment and the gene encoding the Vk2-Cκ light chain, respectively. The CH1 gene segment was then replaced by an oligonucleotide cassette encoding a 20-mer peptide linker with the sequence AGGGS GGGGS GGGGS GGGGS. The two oligonucleotides encoding this linker were 5'- TCAGCGGGTGGCGGTCTGGCGGCGGTGGGAGCGGTGGCGGTGGTTC-TGGCGGTGGTGGTTCGATATCGGTCCACGTACGG-3' and 5'-AATTCCGTACG-TGGACCGATATCGGAACCACCACCGCCAGAACCACCGCCACCGCTCCCACCGCCGCCAGAACCAGCCACCCGC-3', respectively. Finally, the HuCAL-Vk2 gene was inserted *via* EcoRV and BsiWI into the plasmid encoding the HuCAL-VH3-linker fusion, leading to the final gene HuCAL-VH3-Vk2, which encoded the two consensus sequences in the single-chain format VH-linker-VL. The complete coding sequence is shown in Fig. 8.

### ***2.2 Construction of a monovalent phage-display phagemid vector pIG10.3***

Phagemid pIG10.3 (Fig. 9) was constructed in order to create a phage-display system (Winter et al., 1994) for the H3k2 scFv gene. Briefly, the EcoRI/HindIII restriction fragment in the phagemid vector pIG10 (Ge et al., 1995) was replaced by the c-myc followed by an amber codon (which encodes an glutamate in the amber-suppressor strain XL1 Blue and a stop codon in the non-suppressor strain JM83) and a truncated version of the gene III (fusion junction at codon 249, see Lowman et al., 1991) through PCR mutagenesis.

### 2.3 Construction of H-CDR3 libraries

Heavy chain CDR3 libraries of two lengths (10 and 15 amino acids) were constructed using trinucleotide codon containing oligonucleotides (Virnekås et al., 1994) as templates and the oligonucleotides complementing the flanking regions as primers. To concentrate only on the CDR3 structures that appear most often in functional antibodies, we kept the salt-bridge of  $R_{H94}$  and  $D_{H101}$  in the CDR3 loop. For the 15-mer library, both phenylalanine and methionine were introduced at position 100 since these two residues were found to occur quite often in human CDR3s of this length (not shown). For the same reason, valine and tyrosine were introduced at position 102. All other randomized positions contained codons for all amino acids except cysteine, which was not used in the trinucleotide mixture.

The CDR3 libraries of lengths 10 and 15 were generated from the PCR fragments using oligonucleotide templates O3HCDR103T (5'-GATACGGCCGTGTATTA-TTGC GCGCGT (TRI)<sub>6</sub>GATTATTGGGGCCAAGGCACCCTG-3') and O3HCDR153T (5'-GATACGGCCGT GTATTATTGCGCGCGT(TRI)<sub>10</sub>(TTT/ATG)GAT(GTT/TAT)TGGG-GCCAAGGCACCCTG-3'), and primers O3HCDR35 (5'-GATACGGCCGTGTATTA-TTGC-3') and O3HCDR33 (5'-CAGGGTGCCTTGGCCCC-3'), where TRI are trinucleotide mixtures representing all amino acids without cysteine, (TTT/ATG) and (GTT/TAT) are trinucleotide mixtures encoding the amino acids phenylalanine/methionine and valine/tyrosine, respectively. The potential diversity of these libraries was  $4.7 \times 10^7$  and  $3.4 \times 10^{10}$  for 10-mer and 15-mer library, respectively. The library cassettes were first synthesized from PCR amplification of the oligo templates in the presence of both primers: 25 pmol of the oligo template O3HCDR103T or O3HCDR153T, 50 pmol each of the primers O3HCDR35 and O3HCDR33, 20 nmol of dNTP, 10x buffer and 2.5 units of Pfu DNA polymerase (Stratagene) in a total volume of 100  $\mu$ l for 30 cycles (1 minute at 92°C, 1 minute at 62°C and 1 minute at 72°C). A hot-start procedure was used. The resulting mixtures were phenol-extracted, ethanol-precipitated and digested overnight with EagI and Styl. The vector pIG10.3-sch3k2cat, where the EagI-Styl fragment in the vector pIG10.3-sch3k2 encoding the H-CDR3 was replaced by the chloramphenicol acetyltransferase gene (cat) flanked with these two sites, was similarly digested. The digested vector (35  $\mu$ g) was gel-purified and ligated with 100  $\mu$ g of the library cassette overnight at 16°C. The ligation mixtures were isopropanol precipitated, air-dried and the pellets were redissolved in 100  $\mu$ l of ddH<sub>2</sub>O. The ligation was mixed with 1 ml of freshly prepared electrocompetent XL1 Blue on ice. 20 rounds of electroporation were performed and the transformants were diluted in SOC medium, shaken at 37°C for 30 minutes and plated out on large LB plates (Amp/Tet/Glucose)

at 37°C for 6-9 hrs. The number of transformants (library size) was  $3.2 \times 10^7$  and  $2.3 \times 10^7$  for the 10-mer and the 15-mer library, respectively. The colonies were suspended in 2xYT medium (Amp/Tet/Glucose) and stored as glycerol culture.

In order to test the quality of the initial library, phagemids from 24 independent colonies (12 from the 10-mer and 12 from the 15-mer library, respectively) were isolated and analyzed by restriction digestion and sequencing. The restriction analysis of the 24 phagemids indicated the presence of intact vector in all cases. Sequence analysis of these clones (see Fig. 10) indicated that 22 out of 24 contained a functional sequence in their heavy chain CDR3 regions. 1 out of 12 clones of the 10-mer library had a CDR3 of length 9 instead of 10, and 2 out of 12 clones of the 15-mer library had no open reading frame, thereby leading to a non-functional scFv; one of these two clones contained two consecutive inserts, but out of frame (data not shown). All codons introduced were presented in an even distribution.

Expression levels of individual library members were also measured. Briefly, 9 clones from each library were grown in 2xYT medium containing Amp/Tet/0.5% glucose at 37°C overnight. Next day, the cultures were diluted into fresh medium with Amp/Tet. At an  $OD_{600nm}$  of 0.4, the cultures were induced with 1 mM of IPTG and shaken at RT overnight. Then the cell pellets were suspended in 1 ml of PBS buffer + 1 mM of EDTA. The suspensions were sonicated and the supernatants were separated on an SDS-PAGE under reducing conditions, blotted on nylon membrane and detected with anti-FLAG M1 antibody (see Fig. 11). From the nine clones of the 10-mer library, all express the scFv fragments. Moreover, the gene III / scFv fusion proteins were present in all cases. Among the nine clones from the 15-mer library analyzed, 6/9 (67%) led to the expression of both scFv and the gene III/scFv fusion proteins. More importantly, all clones expressing the scFvs and gene III/scFv fusions gave rise to about the same level of expression.

#### **2.4 Biopanning**

Phages displaying the antibody libraries were prepared using standard protocols. Phages derived from the 10-mer library were mixed with phages from the 15-mer library in a ratio of 20:1 ( $1 \times 10^{10}$  cfu/well of the 10-mer and  $5 \times 10^8$  cfu/well of the 15-mer phages, respectively). Subsequently, the phage solution was used for panning in ELISA plates (Maxisorp, Nunc) coated with FITC-BSA (Sigma) at concentration of 100 µg/ml in PBS at 4°C overnight. The antigen-coated wells were blocked with 3% powder milk in PBS and the phage solutions in 1% powder milk were added to each

well and the plate was shaken at RT for 1 hr. The wells were then washed with PBST and PBS (4 times each with shaking at RT for 5 minutes). The bound phages were eluted with 0.1 M triethylamine (TEA) at RT for 10 minutes. The eluted phage solutions were immediately neutralized with 1/2 the volume of 1 M Tris-Cl, pH 7.6. Eluted phage solutions (ca. 450  $\mu$ l) were used to infect 5 ml of XL1 Blue cells at 37°C for 30 min. The infected cultures were then plated out on large LB plates (Amp/Tet/Glucose) and allowed to grow at 37°C until the colonies were visible. The colonies were suspended in 2xYT medium and the glycerol cultures were made as above described. This panning round was repeated twice, and in the third round elution was carried out with addition of fluorescein in a concentration of 100  $\mu$ g/ml in PBS. The enrichment of specific phage antibodies was monitored by panning the initial as well as the subsequent fluorescein-specific sub-libraries against the blocking buffer (Fig. 12). Antibodies with specificity against fluorescein were isolated after 3 rounds of panning.

## 2.5 ELISA measurements

One of the criteria for the successful biopanning is the isolation of individual phage clones that bind to the targeted antigen or hapten. We undertook the isolation of anti-FITC phage antibody clones and characterized them first in a phage ELISA format. After the 3rd round of biopanning (see above), 24 phagemid containing clones were used to inoculate 100  $\mu$ l of 2xYT medium (Amp/Tet/Glucose) in an ELISA plate (Nunc), which was subsequently shaken at 37°C for 5 hrs. 100  $\mu$ l of 2xYT medium (Amp/Tet/1 mM IPTG) were added and shaking was continued for 30 minutes. A further 100  $\mu$ l of 2xYT medium (Amp/Tet) containing the helper phage ( $1 \times 10^9$  cfu/well) was added and shaking was done at RT for 3 hrs. After addition of kanamycin to select for successful helper phage infection, the shaking was continued overnight. The plates were then centrifuged and the supernatants were pipetted directly into ELISA wells coated with 100  $\mu$ l FITC-BSA (100 $\mu$ g/ml) and blocked with milk powder. Washing was performed similarly as during the panning procedure and the bound phages were detected with anti-M13 antibody-POD conjugate (Pharmacia) using soluble POD substrate (Boehringer-Mannheim). Of the 24 clones screened against FITC-BSA, 22 were active in the ELISA (Fig. 13). The initial libraries of similar titer gave rise to no detectable signal. Specificity for fluorescein was measured in a competitive ELISA. Periplasmic fractions of five FITC specific scFvs were prepared as described above. Western blotting indicated that all clones expressed about the same amount of scFv fragment



(data not shown). ELISA was performed as described above, but additionally, the periplasmic fractions were incubated 30 min at RT either with buffer (no inhibition), with 10 mg/ml BSA (inhibition with BSA) or with 10 mg/ml fluorescein (inhibition with fluorescein) before adding to the well. Binding scFv fragment was detected using the anti-FLAG antibody M1. The ELISA signal could only be inhibited, when soluble fluorescein was added, indicating binding of the scFvs was specific for fluorescein (Fig. 14).

## 2.6 Sequence analysis

The heavy chain CDR3 region of 20 clones were sequenced in order to estimate the sequence diversity of fluorescein binding antibodies in the library (Fig. 15). In total, 16 of 20 sequences (80%) were different, showing that the constructed library contained a highly diverse repertoire of fluorescein binders. The CDR3s showed no particular sequence homology, but contained on average 4 arginine residues. This bias towards arginine in fluorescein binding antibodies had already been described by Barbas et al., 1992.

## 2.7 Production

*E. coli* JM83 was transformed with phagemid DNA of 3 selected clones and cultured in 0.5 L 2xYT medium. Induction was carried out with 1 mM IPTG at  $OD_{600nm} = 0.4$  and growth was continued with vigorous shaking at RT overnight. The cells were harvested and pellets were suspended in PBS buffer and sonicated. The supernatants were separated from the cell debris via centrifugation and purified via the BioLogic system (Bio-Rad) by with a POROS<sup>®</sup>MC 20 column (IMAC, PerSeptive Biosystems, Inc.) coupled with an ion-exchange chromatography column. The ion-exchange column was one of the POROS<sup>®</sup>HS, CM or HQ or PI 20 (PerSeptive Biosystems, Inc.) depended on the theoretical pI of the scFv being purified. The pH of all the buffers was adjusted to one unit lower or higher than the pI of the scFv being purified throughout. The sample was loaded onto the first IMAC column, washed with 7 column volumes of 20 mM sodium phosphate, 1 M NaCl and 10 mM imidazole. This washing was followed by 7 column volumes of 20 mM sodium phosphate and 10 mM imidazole. Then 3 column volumes of an imidazole gradient (10 to 250 mM) were applied and the eluent was connected directly to the ion-exchanger. Nine column volumes of isocratic washing with 250 mM imidazole was followed by 15 column volumes of 250 mM to 100 mM and 7 column volumes of an imidazole / NaCl gradient (100 to 10 mM imidazole, 0 to 1 M NaCl). The flow rate was 5 ml/min. The purity of scFv fragments was checked by SDS-PAGE Coomassie

staining (Fig. 16). The concentration of the fragments was determined from the absorbance at 280 nm using the theoretically determined extinction coefficient (Gill & von Hippel, 1989). The scFv fragments could be purified to homogeneity (see Fig. 16). The yield of purified fragments ranged from 5 to 10 mg/L/OD.

### **Example 3: HuCAL H3 $\kappa$ 2 Library Against a Collection of Antigens**

In order to test the library used in Example 2 further, a new selection procedure was carried out using a variety of antigens comprising  $\beta$ -estradiol, testosterone, Lewis-Y epitope (LeY), interleukin-2 (IL-2), lymphotoxin-B (LT- $\beta$ ), E-selectin ligand-1 (ESL-1), and BSA.

#### **3.1 Biopanning**

The library and all procedures were identical to those described in Example 2. The ELISA plates were coated with  $\beta$ -estradiol-BSA (100  $\mu$ g/ml), testosterone-BSA (100  $\mu$ g/ml), LeY-BSA (20  $\mu$ g/ml) IL-2 (20  $\mu$ g/ml), ESL-1 (20  $\mu$ g/ml) and BSA (100  $\mu$ g/ml), LT- $\beta$  (denatured protein, 20  $\mu$ g/ml). In the first two rounds, bound phages were eluted with 0.1 M triethylamine (TEA) at RT for 10 minutes. In the case of BSA, elution after three rounds of panning was carried out with addition of BSA in a concentration of 100  $\mu$ g/ml in PBS. In the case of the other antigens, third round elution was done with 0.1 M triethylamine. In all cases except LeY, enrichment of binding phages could be seen (Figure 17). Moreover, a repetition of the biopanning experiment using only the 15-mer library resulted in the enrichment of LeY-binding phages as well (data not shown).

#### **3.2. ELISA measurements**

Clones binding to  $\beta$ -estradiol, testosterone, LeY, LT- $\beta$ , ESL-1 and BSA were further analyzed and characterized as described in Example 2 for FITC. ELISA data for anti- $\beta$ -estradiol and anti-ESL-1 antibodies are shown in Fig. 18. In one experiment, selectivity and cross-reactivity of binding scFv fragments were tested. For this purpose, an ELISA plate was coated with FITC, testosterone,  $\beta$ -estradiol, BSA, and ESL-1, with 5 wells for each antigen arranged in 5 rows, and 5 antibodies, one against each of the antigens, were screened against each of the antigens. Fig. 19

shows the specific binding of the antibodies to the antigen it was selected for, and the low cross-reactivity with the other four antigens.

### **3.3 Sequence analysis**

The sequencing data of several clones against  $\beta$ -estradiol (34 clones), testosterone (12 clones), LT- $\beta$  (23 clones), ESL-1 (34 clones), and BSA (10 clones) are given in Figures 20 to 24.

### **Example 4: Vector Construction**

To be able to take advantage of the modularity of the consensus gene repertoire, a vector system had to be constructed which could be used in phage display screening of HuCAL libraries and subsequent optimization procedures. Therefore, all necessary vector elements such as origins of single-stranded or double-stranded replication, promotor/operator, repressor or terminator elements, resistance genes, potential recombination sites, gene III for display on filamentous phages, signal sequences, or detection tags had to be made compatible with the restriction site pattern of the modular consensus genes. Figure 25 shows a schematic representation of the pCAL vector system and the arrangement of vector modules and restriction sites therein. Figure 25a shows a list of all restriction sites which are already incorporated into the consensus genes or the vector elements as part of the modular system or which are not yet present in the whole system. The latter could be used in a later stage for the introduction of or within new modules.

#### **4.1 Vector modules**

A series of vector modules was constructed where the restriction sites flanking the gene sub-elements of the HuCAL genes were removed, the vector modules themselves being flanked by unique restriction sites. These modules were constructed either by gene synthesis or by mutagenesis of templates. Mutagenesis was done by add-on PCR, by site-directed mutagenesis (Kunkel et al., 1991) or multisite oligonucleotide-mediated mutagenesis (Sutherland et al., 1995; Perlak, 1990) using a PCR-based assembly method.

Figure 26 contains a list of the modules constructed. Instead of the terminator module M9 (HindIII-*lpp*-PacI), a larger cassette M9II was prepared to introduce FseI as additional restriction site. M9II can be cloned via HindIII/BsrGI.

All vector modules were characterized by restriction analysis and sequencing. In the case of module M11-II, sequencing of the module revealed a two-base difference in positions 164/65 compared to the sequence database of the template. These two different bases (CA → GC) created an additional BanII site. Since the same two-base difference occurs in the f1 origin of other bacteriophages, it can be assumed that the two-base difference was present in the template and not created by mutagenesis during cloning. This BanII site was removed by site-directed mutagenesis, leading to module M11-III. The BssSI site of module M14 could initially not be removed without impact on the function of the ColE1 origin, therefore M14-Ext2 was used for cloning of the first pCAL vector series. Figures 29 to 34 are showing the functional maps and sequences of the modules used for assembly of the modular vector pCAL4 (see below). The functional maps and sequences of additional modules can be found in Figure 35a. Figure 35b contains a list of oligonucleotides and primers used for the synthesis of the modules.

#### **4.2 Cloning vector pMCS**

To be able to assemble the individual vector modules, a cloning vector pMCS containing a specific multi-cloning site (MCS) was constructed. First, an MCS cassette (Fig. 27) was made by gene synthesis. This cassette contains all those restriction sites in the order necessary for the sequential introduction of all vector modules and can be cloned via the 5'-HindIII site and a four base overhang at the 3'-end compatible with an AatII site. The vector pMCS (Figure 28) was constructed by digesting pUC19 with AatII and HindIII, isolating the 2174 base pair fragment containing the *bla* gene and the ColE1 origin, and ligating the MCS cassette.

#### **4.3 Cloning of modular vector pCAL4**

This was cloned step by step by restriction digest of pMCS and subsequent ligation of the modules M1 (via AatII/XbaI), M7III (via EcoRI/HindIII), and M9II (via HindIII/BsrGI), and M11-II (via BsrGI/NheI). Finally, the *bla* gene was replaced by the *cat* gene module M17 (via AatII/BglII), and the wild type ColE1 origin by module M14-Ext2 (via BglII/NheI). Figure 35 is showing the functional map and the sequence of pCAL4.

#### **4.4 Cloning of low-copy number plasmid vectors pCALO**

A series of low-copy number plasmid vectors was constructed in a similar way using the p15A module M12 instead of the ColE1 module M14-Ext2. Figure 35a is showing the functional maps and sequences of the vectors pCALO1 to pCALO3.

### **Example 5: Construction of a HuCAL scFv Library**

#### **5.1. Cloning of all 49 HuCAL scFv fragments**

All 49 combinations of the 7 HuCAL-VH and 7 HuCAL-VL consensus genes were assembled as described for the HuCAL VH3-V $\kappa$ 2 scFv in Example 2 and inserted into the vector pBS12, a modified version of the pLisc series of antibody expression vectors (Skerra et al., 1991).

#### **5.2 Construction of a CDR cloning cassette**

For replacement of CDRs, a universal  $\beta$ -lactamase cloning cassette was constructed having a multi-cloning site at the 5'-end as well as at the 3'-end. The 5'-multi-cloning site comprises all restriction sites adjacent to the 5'-end of the HuCAL VH and VL CDRs, the 3'-multi-cloning site comprises all restriction sites adjacent to the 3' end of the HuCAL VH and VL CDRs. Both 5'- and 3'-multi-cloning site were prepared as cassettes via add-on PCR using synthetic oligonucleotides as 5'- and 3'-primers using wild type  $\beta$ -lactamase gene as template. Figure 36 shows the functional map and the sequence of the cassette bla-MCS.

#### **5.3. Preparation of VL-CDR3 library cassettes**

The VL-CDR3 libraries comprising 7 random positions were generated from the PCR fragments using oligonucleotide templates V $\kappa$ 1&V $\kappa$ 3, V $\kappa$ 2 and V $\kappa$ 4 and primers O\_K3L\_5 and O\_K3L\_3 (Fig. 37) for the V $\kappa$  genes, and V $\lambda$  and primers O\_L3L\_5 (5'-GCAGAAGGCGAACGTCC-3') and O\_L3LA\_3 (Fig. 38) for the V $\lambda$  genes. Construction of the cassettes was performed as described in Example 2.3.

#### ***5.4 Cloning of HuCAL scFv genes with VL-CDR3 libraries***

Each of the 49 single-chains was subcloned into pCAL4 via XbaI/EcoRI and the VL-CDR3 replaced by the  $\beta$ -lactamase cloning cassette via BbsI/MscI, which was then replaced by the corresponding VL-CDR3 library cassette synthesized as described above. This CDR replacement is described in detail in Example 2.3 where the cat gene was used.

#### ***5.5 Preparation of VH-CDR3 library cassette***

The VH-CDR3 libraries were designed and synthesized as described in Example 2.3.

#### ***5.6 Cloning of HuCAL scFv genes with VL- and VH-CDR3 libraries***

Each of the 49 single-chain VL-CDR3 libraries was digested with BssHII/StyI to replace VH-CDR3. The "dummy" cassette digested with BssHII/StyI was inserted, and was then replaced by a corresponding VH-CDR3 library cassette synthesized as described above.

#### **Example 6: Expression tests**

Expression and toxicity studies were performed using the scFv format VH-linker-VL. All 49 combinations of the 7 HuCAL-VH and 7 HuCAL-VL consensus genes assembled as described in Example 5 were inserted into the vector pBS13, a modified version of the pLisc series of antibody expression vectors (Skerra et al., 1991). A map of this vector is shown in Fig. 39.

*E. coli* JM83 was transformed 49 times with each of the vectors and stored as glycerol stock. Between 4 and 6 clones were tested simultaneously, always including the clone H3k2, which was used as internal control throughout. As additional control, the McPC603 scFv fragment (Knappik & Plückthun, 1995) in pBS13 was expressed under identical conditions. Two days before the expression test was performed, the clones were cultivated on LB plates containing 30  $\mu$ g/ml chloramphenicol and 60 mM glucose. Using this plates an 3 ml culture (LB medium

containing 90  $\mu$ g chloramphenicol and 60 mM glucose) was inoculated overnight at 37 °C. Next day the overnight culture was used to inoculate 30 ml LB medium containing chloramphenicol (30  $\mu$ g/ml). The starting OD<sub>600nm</sub> was adjusted to 0.2 and a growth temperature of 30 °C was used. The physiology of the cells was monitored by measuring every 30 minutes for 8 to 9 hours the optical density at 600 nm. After the culture reached an OD<sub>600nm</sub> of 0.5, antibody expression was induced by adding IPTG to a final concentration of 1 mM. A 5 ml aliquot of the culture was removed after 2 h of induction in order to analyze the antibody expression. The cells were lysed and the soluble and insoluble fractions of the crude extract were separated as described in Knappik & Plückthun, 1995. The fractions were assayed by reducing SDS-PAGE with the samples normalized to identical optical densities. After blotting and immunostaining using the  $\alpha$ -FLAG antibody M1 as the first antibody (see Ge et al., 1994) and an Fc-specific anti-mouse antiserum conjugated to alkaline phosphatase as the second antibody, the lanes were scanned and the intensities of the bands of the expected size (appr. 30 kDa) were quantified densitometrically and tabulated relative to the control antibody (see Fig. 40).

## Example 7: Optimization of Fluorescein Binders

### 7.1. Construction of L-CDR3 and H-CDR2 library cassettes

A L-CDR3 library cassette was prepared from the oligonucleotide template CDR3L (5'-TGGAAGCTGAAGACGTGGGCGTGTATTATTGCCAGCAG(TR5)(TRI)<sub>4</sub>CCG(TRI)-TTTGGCCAGGGTACGAAAGTT-3') and primer 5'-AACTTTCGTACCCTGGCC-3' for synthesis of the complementary strand, where (TRI) was a trinucleotide mixture representing all amino acids except Cys, (TR5) comprised a trinucleotide mixture representing the 5 codons for Ala, Arg, His, Ser, and Tyr.

A H-CDR2 library cassette was prepared from the oligonucleotide template CDRsH (5'-AGGGTCTCGAGTGGGTGAGC(TRI)ATT(TRI)<sub>2,3</sub>(6)<sub>2</sub>(TRI)ACC(TRI)TATGCGGATAGCGTGAAAGGCCGTTTTACCATTTACGTGATAATTCGAAAAACACCA-3'), and primer 5'-TGGTGTTTTTCGAATTATCA-3' for synthesis of the complementary strand, where (TRI) was a trinucleotide mixture representing all amino acids except Cys, (6) comprised the incorporation of (A/G) (A/C/G) T, resulting in the formation of 6 codons for Ala, Asn, Asp, Gly, Ser, and Thr, and the length distribution being obtained by performing one substoichiometric coupling of the (TRI) mixture during synthesis, omitting the capping step normally used in DNA synthesis.

DNA synthesis was performed on a 40 nmole scale, oligos were dissolved in TE buffer, purified via gel filtration using spin columns (S-200), and the DNA concentration determined by OD measurement at 260 nm (OD 1.0 = 40  $\mu$ g/ml).

10 nmole of the oligonucleotide templates and 12 nmole of the corresponding primers were mixed and annealed at 80°C for 1 min, and slowly cooled down to 37°C within 20 to 30 min. The fill-in reaction was performed for 2 h at 37°C using Klenow polymerase (2.0  $\mu$ l) and 250 nmole of each dNTP. The excess of dNTPs was removed by gel filtration using Nick-Spin columns (Pharmacia), and the double-stranded DNA digested with BbsI/MscI (L-CDR3), or XhoI/SfuI (H-CDR2) over night at 37°C. The cassettes were purified via Nick-Spin columns (Pharmacia), the concentration determined by OD measurement, and the cassettes aliquoted (15 pmole) for being stored at -80°C.

## 7.2 Library cloning:

DNA was prepared from the collection of FITC binding clones obtained in Example 2 (approx.  $10^4$  to clones). The collection of scFv fragments was isolated via XbaI/EcoRI digest. The vector pCAL4 (100 fmole, 10  $\mu$ g) described in Example 4.3 was similarly digested with XbaI/EcoRI, gel-purified and ligated with 300 fmole of the scFv fragment collection over night at 16°C. The ligation mixture was isopropanol precipitated, air-dried, and the pellets were redissolved in 100  $\mu$ l of dd H<sub>2</sub>O. The ligation mixture was mixed with 1 ml of freshly prepared electrocompetent SCS 101 cells (for optimization of L-CDR3), or XL1 Blue cells (for optimization of H-CDR2) on ice. One round of electroporation was performed and the transformants were eluted in SOC medium, shaken at 37°C for 30 minutes, and an aliquot plated out on LB plates (Amp/Tet/Glucose) at 37°C for 6-9 hrs. The number of transformants was  $5 \times 10^4$ .

Vector DNA (100  $\mu$ g) was isolated and digested (sequence and restriction map of scH3k2 see Figure 8) with BbsI/MscI for optimization of L-CDR3, or XhoI/NspV for optimization of H-CDR2. 10  $\mu$ g of purified vector fragments (5 pmole) were ligated with 15 pmole of the L-CDR3 or H-CDR2 library cassettes over night at 16°C. The ligation mixtures were isopropanol precipitated, air-dried, and the pellets were redissolved in 100  $\mu$ l of dd H<sub>2</sub>O. The ligation mixtures were mixed with 1 ml of freshly prepared electrocompetent XL1 Blue cells on ice. Electroporation was performed and the transformants were eluted in SOC medium and shaken at 37°C for 30 minutes. An aliquot was plated out on LB plates (Amp/Tet/Glucose) at 37°C for 6-9



hrs. The number of transformants (library size) was greater than  $10^8$  for both libraries. The libraries were stored as glycerol cultures.

### **7.3. Biopanning**

This was performed as described for the initial H3κ2 H-CDR3 library in Example 2.1. Optimized scFvs binding to FITC could be characterized and analyzed as described in Example 2.2 and 2.3, and further rounds of optimization could be made if necessary.

### References

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Table 1A: Human kappa germline gene segments

| Used Name <sup>1</sup> | Reference <sup>2</sup> | Family <sup>3</sup> | Germline genes <sup>4</sup>                  |
|------------------------|------------------------|---------------------|--|
| Vk1-1                  | 9                      | 1                   | O8; O18; DPK1                                |
| Vk1-2                  | 1                      | 1                   | L14; DPK2                                    |
| Vk1-3                  | 2                      | 1                   | L15(1); HK101; HK146; HK189                  |
| Vk1-4                  | 9                      | 1                   | L11  |
| Vk1-5                  | 2                      | 1                   | A30  |
| Vk1-6                  | 1                      | 1                   | LFVK5  |
| Vk1-7                  | 1                      | 1                   | LFVK431                                      |
| Vk1-8                  | 1                      | 1                   | L1; HK137                                    |
| Vk1-9                  | 1                      | 1                   | A20; DPK4                                    |
| Vk1-10                 | 1                      | 1                   | L18; Va"                                     |
| Vk1-11                 | 1                      | 1                   | L4; L18; Va'; V4a                            |
| Vk1-12                 | 2                      | 1                   | L5; L19(1); Vb; Vb4; DPK5; L19(2); Vb"; DPK6 |
| Vk1-13                 | 2                      | 1                   | L15(2); HK134; HK166; DPK7                   |
| Vk1-14                 | 8                      | 1                   | L8; Vd; DPK8                                 |
| Vk1-15                 | 8                      | 1                   | L9; Ve                                       |
| Vk1-16                 | 1                      | 1                   | L12(1); HK102; V1                            |
| Vk1-17                 | 2                      | 1                   | L12(2)                                       |
| Vk1-18                 | 1                      | 1                   | O12a (V3b)                                   |
| Vk1-19                 | 6                      | 1                   | O2; O12; DPK9                                |
| Vk1-20                 | 2                      | 1                   | L24; Ve"; V13; DPK10                         |
| Vk1-21                 | 1                      | 1                   | O4; O14                                      |
| Vk1-22                 | 2                      | 1                   | L22  |
| Vk1-23                 | 2                      | 1                   | L23  |
| Vk2-1                  | 1                      | 2                   | A2; DPK12                                    |
| Vk2-2                  | 6                      | 2                   | O1; O11(1); DPK13                            |
| Vk2-3                  | 6                      | 2                   | O12(2); V3a                                  |
| Vk2-4                  | 2                      | 2                   | L13  |
| Vk2-5                  | 1                      | 2                   | DPK14  |
| Vk2-6                  | 4                      | 2                   | A3; A19; DPK15                               |
| Vk2-7                  | 4                      | 2                   | A29; DPK27                                   |
| Vk2-8                  | 4                      | 2                   | A13  |
| Vk2-9                  | 1                      | 2                   | A23  |

Table 1A: (continued)

| Used Name <sup>1</sup> | Reference <sup>2</sup> | Family <sup>3</sup> | Germline genes <sup>4</sup>                      |
|------------------------|------------------------|---------------------|--|
| Vk2-10                 | 4                      | 2                   | A7; DPK17  |
| Vk2-11                 | 4                      | 2                   | A17; DPK18                                       |
| Vk2-12                 | 4                      | 2                   | A1; DPK19  |
| Vk3-1                  | 11                     | 3                   | A11; humkv305; DPK20                             |
| Vk3-2                  | 1                      | 3                   | L20; Vg"   |
| Vk3-3                  | 2                      | 3                   | L2; L16; humkv328; humkv328h2; humkv328h5; DPK21 |
| Vk3-4                  | 11                     | 3                   | A27; humkv325; VkRF; DPK22                       |
| Vk3-5                  | 2                      | 3                   | L25; DPK23                                       |
| Vk3-6                  | 2                      | 3                   | L10(1)   |
| Vk3-7                  | 7                      | 3                   | L10(2)   |
| Vk3-8                  | 7                      | 3                   | L6; Vg   |
| Vk4-1                  | 3                      | 4                   | B3; VkIV; DPK24                                  |
| Vk5-1                  | 10                     | 5                   | B2; EV15   |
| Vk6-1                  | 12                     | 6                   | A14; DPK25                                       |
| Vk6-2                  | 12                     | 6                   | A10; A26; DPK26                                  |
| Vk7-1                  | 5                      | 7                   | B1   |

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Table 1B: Human lambda germline gene segments

| Used Name <sup>1</sup> | Reference <sup>2</sup> | Family <sup>3</sup> | Germline genes <sup>4</sup> |
|------------------------|------------------------|---------------------|-----------------------------|
| DPL1                   | 1                      | 1                   |                             |
| DPL2                   | 1                      | 1                   | HUMLV1L1                    |
| DPL3                   | 1                      | 1                   | HUMLV122                    |
| DPL4                   | 1                      | 1                   | VLAMBDA 1.1                 |
| HUMLV117               | 2                      | 1                   |                             |
| DPL5                   | 1                      | 1                   | HUMLV117D                   |
| DPL6                   | 1                      | 1                   |                             |
| DPL7                   | 1                      | 1                   | IGLV1S2                     |
| DPL8                   | 1                      | 1                   | HUMLV1042                   |
| DPL9                   | 1                      | 1                   | HUMLV101                    |
| DPL10                  | 1                      | 2                   |                             |
| VLAMBDA 2.1            | 3                      | 2                   |                             |
| DPL11                  | 1                      | 2                   |                             |
| DPL12                  | 1                      | 2                   |                             |
| DPL13                  | 1                      | 2                   |                             |
| DPL14                  | 1                      | 2                   |                             |
| DPL16                  | 1                      | 3                   | Humlv418; IGLV3S1           |
| DPL23                  | 1                      | 3                   | VI III.1                    |
| Humlv318               | 4                      | 3                   |                             |
| DPL18                  | 1                      | 7                   | 4A; HUMIGLVA                |
| DPL19                  | 1                      | 7                   |                             |
| DPL21                  | 1                      | 8                   | VL8.1                       |
| HUMLV801               | 5                      | 8                   |                             |
| DPL22                  | 1                      | 9                   |                             |
| DPL24                  | 1                      | unassigned          | VLAMBDA N.2                 |
| gVLX-4.4               | 6                      | 10                  |                             |

Table 1C: Human heavy chain germline gene segments

| Used Name <sup>1</sup> | Reference <sup>2</sup> | Family <sup>3</sup> | Germline genes <sup>4</sup> |
|------------------------|------------------------|---------------------|-----------------------------|
| VH1-12-1               | 19                     | 1                   | DP10; DA-2; DA-6            |
| VH1-12-8               | 22                     | 1                   | RR.VH1.2                    |
| VH1-12-2               | 6                      | 1                   | hv1263                      |
| VH1-12-9               | 7                      | 1                   | YAC-7; RR.VH1.1; 1-69       |
| VH1-12-3               | 19                     | 1                   | DP3                         |
| VH1-12-4               | 19                     | 1                   | DP21; 4d275a; VH7a          |
| VH1-12-5               | 18                     | 1                   | I-4.1b; V1-4.1b             |
| VH1-12-6               | 21                     | 1                   | 1D37; VH7b ; 7-81; YAC-10   |
| VH1-12-7               | 19                     | 1                   | DP14; VH1GRR; V1-18         |
| VH1-13-1               | 10                     | 1                   | 71-5; DP2                   |
| VH1-13-2               | 10                     | 1                   | E3-10                       |
| VH1-13-3               | 19                     | 1                   | DP1                         |
| VH1-13-4               | 12                     | 1                   | V35                         |
| VH1-13-5               | 8                      | 1                   | V1-2b                       |
| VH1-13-6               | 18                     | 1                   | I-2; DP75                   |
| VH1-13-7               | 21                     | 1                   | V1-2                        |
| VH1-13-8               | 19                     | 1                   | DP8                         |
| VH1-13-9               | 3                      | 1                   | 1-1                         |
| VH1-13-10              | 19                     | 1                   | DP12                        |
| VH1-13-11              | 15                     | 1                   | V13C                        |
| VH1-13-12              | 18                     | 1                   | I-3b; DP25; V1-3b           |
| VH1-13-13              | 3                      | 1                   | 1-92                        |
| VH1-13-14              | 18                     | 1                   | I-3; V1-3                   |
| VH1-13-15              | 19                     | 1                   | DP15; V1-8                  |
| VH1-13-16              | 3                      | 1                   | 21-2; 3-1; DP7; V1-46       |
| VH1-13-17              | 16                     | 1                   | HG3                         |
| VH1-13-18              | 19                     | 1                   | DP4; 7-2; V1-45             |
| VH1-13-19              | 27                     | 1                   | COS 5                       |
| VH1-1X-1               | 19                     | 1                   | DP5; 1-24P                  |
| VH2-21-1               | 18                     | 2                   | II-5b                       |
| VH2-31-1               | 2                      | 2                   | VH2S12-1                    |
| VH2-31-2               | 2                      | 2                   | VH2S12-7                    |
| VH2-31-3               | 2                      | 2                   | VH2S12-9; DP27              |
| VH2-31-4               | 2                      | 2                   | VH2S12-10                   |
| VH2-31-5               | 14                     | 2                   | V2-26; DP26; 2-26           |
| VH2-31-6               | 15                     | 2                   | VF2-26                      |

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Table 1C: (continued)

| Used Name <sup>1</sup> | Reference <sup>2</sup> | Family <sup>3</sup> | Germline genes <sup>4</sup>                        |
|------------------------|------------------------|---------------------|--|
| VH2-31-7               | 19                     | 2                   | DP28; DA-7   |
| VH2-31-14              | 7                      | 2                   | YAC-3; 2-70  |
| VH2-31-8               | 2                      | 2                   | VH2S12-5   |
| VH2-31-9               | 2                      | 2                   | VH2S12-12  |
| VH2-31-10              | 18                     | 2                   | II-5; V2-5   |
| VH2-31-11              | 2                      | 2                   | VH2S12-2; VH2S12-8                                 |
| VH2-31-12              | 2                      | 2                   | VH2S12-4; VH2S12-6                                 |
| VH2-31-13              | 2                      | 2                   | VH2S12-14  |
| VH3-11-1               | 13                     | 3                   | v65-2; DP44  |
| VH3-11-2               | 19                     | 3                   | DP45   |
| VH3-11-3               | 3                      | 3                   | 13-2; DP48   |
| VH3-11-4               | 19                     | 3                   | DP52   |
| VH3-11-5               | 14                     | 3                   | v3-13  |
| VH3-11-6               | 19                     | 3                   | DP42   |
| VH3-11-7               | 3                      | 3                   | 8-1B; YAC-5; 3-66                                  |
| VH3-11-8               | 14                     | 3                   | V3-53  |
| VH3-13-1               | 3                      | 3                   | 22-2B; DP35; V3-11                                 |
| VH3-13-5               | 19                     | 3                   | DP59; VH19; V3-35                                  |
| VH3-13-6               | 25                     | 3                   | f1-p1; DP61  |
| VH3-13-7               | 19                     | 3                   | DP46; GL-SJ2; COS 8; hv3005; hv3005f3; 3d21b; 56p1 |
| VH3-13-8               | 24                     | 3                   | VH26   |
| VH3-13-9               | 5                      | 3                   | vh26c  |
| VH3-13-10              | 19                     | 3                   | DP47; VH26; 3-23                                   |
| VH3-13-11              | 3                      | 3                   | 1-91   |
| VH3-13-12              | 19                     | 3                   | DP58   |
| VH3-13-13              | 3                      | 3                   | 1-9III; DP49; 3-30; 3d28.1                         |
| VH3-13-14              | 24                     | 3                   | 3019B9; DP50; 3-33; 3d277                          |
| VH3-13-15              | 27                     | 3                   | COS 3  |
| VH3-13-16              | 19                     | 3                   | DP51   |
| VH3-13-17              | 16                     | 3                   | H11  |
| VH3-13-18              | 19                     | 3                   | DP53; COS 6; 3-74; DA-8                            |
| VH3-13-19              | 19                     | 3                   | DP54; VH3-11; V3-7                                 |
| VH3-13-20              | 14                     | 3                   | V3-64; YAC-6                                       |
| VH3-13-21              | 14                     | 3                   | V3-48  |
| VH3-13-22              | 14                     | 3                   | V3-43; DP33  |
| VH3-13-23              | 14                     | 3                   | V3-33  |



Table 1C: (continued)

| Used Name <sup>1</sup> | Reference <sup>2</sup> | Family <sup>3</sup> | Germline genes <sup>4</sup>  |
|------------------------|------------------------|---------------------|--|
| VH3-13-24              | 14                     | 3                   | V3-21; DP77  |
| VH3-13-25              | 14                     | 3                   | V3-20; DP32  |
| VH3-13-26              | 14                     | 3                   | V3-9; DP31   |
| VH3-14-1               | 3                      | 3                   | 12-2; DP29; 3-72; DA-3   |
| VH3-14-4               | 7                      | 3                   | YAC-9; 3-73; MTGL  |
| VH3-14-2               | 4                      | 3                   | VHD26  |
| VH3-14-3               | 19                     | 3                   | DP30   |
| VH3-1X-1               | 1                      | 3                   | LSG8.1; LSG9.1; LSG10.1; HUM12IGVH; HUM13IGVH                                    |
| VH3-1X-2               | 1                      | 3                   | LSG11.1; HUM4IGVH  |
| VH3-1X-3               | 3                      | 3                   | 9-1; DP38; LSG7.1; RCG1.1; LSG1.1; LSG3.1; LSG5.1; HUM15IGVH; HUM2IGVH; HUM9IGVH |
| VH3-1X-4               | 1                      | 3                   | LSG4.1   |
| VH3-1X-5               | 1                      | 3                   | LSG2.1   |
| VH3-1X-6               | 1                      | 3                   | LSG6.1; HUM10IGVH  |
| VH3-1X-7               | 18                     | 3                   | 3-15; V3-15  |
| VH3-1X-8               | 1                      | 3                   | LSG12.1; HUM5IGVH  |
| VH3-1X-9               | 14                     | 3                   | V3-49  |
| VH4-11-1               | 22                     | 4                   | Tou-VH4.21   |
| VH4-11-2               | 17                     | 4                   | VH4.21; DP63; VH5; 4d76; V4-34   |
| VH4-11-3               | 23                     | 4                   | 4.44   |
| VH4-11-4               | 23                     | 4                   | 4.44.3   |
| VH4-11-5               | 23                     | 4                   | 4.36   |
| VH4-11-6               | 23                     | 4                   | 4.37   |
| VH4-11-7               | 18                     | 4                   | IV-4; 4.35; V4-4   |
| VH4-11-8               | 17                     | 4                   | VH4.11; 3d197d; DP71; 58p2   |
| VH4-11-9               | 20                     | 4                   | H7   |
| VH4-11-10              | 20                     | 4                   | H8   |
| VH4-11-11              | 20                     | 4                   | H9   |
| VH4-11-12              | 17                     | 4                   | VH4.16   |
| VH4-11-13              | 23                     | 4                   | 4.38   |
| VH4-11-14              | 17                     | 4                   | VH4.15   |
| VH4-11-15              | 11                     | 4                   | 58   |
| VH4-11-16              | 10                     | 4                   | 71-4; V4-59  |
| VH4-21-1               | 11                     | 4                   | 11   |
| VH4-21-2               | 17                     | 4                   | VH4.17; VH4.23; 4d255; 4.40; DP69  |
| VH4-21-3               | 17                     | 4                   | VH4.19; 79; V4-4b  |

Table 1C: (continued)

| Used Name <sup>1</sup> | Reference <sup>2</sup> | Family <sup>3</sup> | Germline genes <sup>4</sup>  |
|------------------------|------------------------|---------------------|--|
| VH4-21-4               | 19                     | 4                   | DP70; 4d68; 4.41   |
| VH4-21-5               | 19                     | 4                   | DP67; VH4-4B   |
| VH4-21-6               | 17                     | 4                   | VH4.22; VHSP; VH-JA  |
| VH4-21-7               | 17                     | 4                   | VH4.13; 1-9II; 12G-1; 3d28d; 4.42; DP68; 4-28  |
| VH4-21-8               | 26                     | 4                   | hv4005; 3d24d  |
| VH4-21-9               | 17                     | 4                   | VH4.14   |
| VH4-31-1               | 23                     | 4                   | 4.34; 3d230d; DP78   |
| VH4-31-2               | 23                     | 4                   | 4.34.2   |
| VH4-31-3               | 19                     | 4                   | DP64; 3d216d   |
| VH4-31-4               | 19                     | 4                   | DP65; 4-31; 3d277d   |
| VH4-31-5               | 23                     | 4                   | 4.33; 3d75d  |
| VH4-31-6               | 20                     | 4                   | H10  |
| VH4-31-7               | 20                     | 4                   | H11  |
| VH4-31-8               | 23                     | 4                   | 4.31   |
| VH4-31-9               | 23                     | 4                   | 4.32   |
| VH4-31-10              | 20                     | 4                   | 3d277d   |
| VH4-31-11              | 20                     | 4                   | 3d216d   |
| VH4-31-12              | 20                     | 4                   | 3d279d   |
| VH4-31-13              | 17                     | 4                   | VH4.18; 4d154; DP79  |
| VH4-31-14              | 8                      | 4                   | V4-39  |
| VH4-31-15              | 11                     | 4                   | 2-1; DP79  |
| VH4-31-16              | 23                     | 4                   | 4.30   |
| VH4-31-17              | 17                     | 4                   | VH4.12   |
| VH4-31-18              | 10                     | 4                   | 71-2; DP66   |
| VH4-31-19              | 23                     | 4                   | 4.39   |
| VH4-31-20              | 8                      | 4                   | V4-61  |
| VH5-12-1               | 9                      | 5                   | VH251; DP73; VHVCW; 51-R1; VHVLB; VHVCB; VHVTI;<br>VHVAU; VHVBK; VhAU; V5-51             |
| VH5-12-2               | 17                     | 5                   | VHVJB  |
| VH5-12-3               | 3                      | 5                   | 1-v; DP80; 5-78  |
| VH5-12-4               | 9                      | 5                   | VH32; VHVRG; VHVMW; 5-2R1  |
| VH6-35-1               | 4                      | 6                   | VHVI; VH6; VHVIIS; VHVITE; VHVJJB; VHVICH; VHVICW;<br>VHVIBLK; VHVIMW; DP74; 6-1G1; V6-1 |

Table 2A: rearranged human kappa sequences

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| III-3R            | 108             | 1                            | O8                         | 1                              | 1,1%                             | 70                     |
| No.86             | 109             | 1                            | O8                         | 3                              | 3,2%                             | 80                     |
| AU                | 108             | 1                            | O8                         | 6                              | 6,3%                             | 103                    |
| ROY               | 108             | 1                            | O8                         | 6                              | 6,3%                             | 43                     |
| IC4               | 108             | 1                            | O8                         | 6                              | 6,3%                             | 70                     |
| HIV-B26           | 106             | 1                            | O8                         | 3                              | 3,2%                             | 8                      |
| GRI               | 108             | 1                            | O8                         | 8                              | 8,4%                             | 30                     |
| AG                | 106             | 1                            | O8                         | 8                              | 8,6%                             | 116                    |
| REI               | 108             | 1                            | O8                         | 9                              | 9,5%                             | 86                     |
| CLL PATIENT 16    | 88              | 1                            | O8                         | 2                              | 2,3%                             | 122                    |
| CLL PATIENT 14    | 87              | 1                            | O8                         | 2                              | 2,3%                             | 122                    |
| CLL PATIENT 15    | 88              | 1                            | O8                         | 2                              | 2,3%                             | 122                    |
| GM4672            | 108             | 1                            | O8                         | 11                             | 11,6%                            | 24                     |
| HUM. YFC51.1      | 108             | 1                            | O8                         | 12                             | 12,6%                            | 110                    |
| LAY               | 108             | 1                            | O8                         | 12                             | 12,6%                            | 48                     |
| HIV-b13           | 106             | 1                            | O8                         | 9                              | 9,7%                             | 8                      |
| MAL-NaCl          | 108             | 1                            | O8                         | 13                             | 13,7%                            | 102                    |
| STRAb SA-1A       | 108             | 1                            | O2                         | 0                              | 0,0%                             | 120                    |
| HuVHCAMP          | 108             | 1                            | O8                         | 13                             | 13,7%                            | 100                    |
| CRO               | 108             | 1                            | O2                         | 10                             | 10,5%                            | 30                     |
| Am107             | 108             | 1                            | O2                         | 12                             | 12,6%                            | 108                    |
| WALKER            | 107             | 1                            | O2                         | 4                              | 4,2%                             | 57                     |
| III-2R            | 109             | 1                            | A20                        | 0                              | 0,0%                             | 70                     |
| FOG1-A4           | 107             | 1                            | A20                        | 4                              | 4,2%                             | 41                     |
| HK137             | 95              | 1                            | L1                         | 0                              | 0,0%                             | 10                     |
| CEA4-8A           | 107             | 1                            | O2                         | 7                              | 7,4%                             | 41                     |
| Va'               | 95              | 1                            | L4                         | 0                              | 0,0%                             | 90                     |
| TR1.21            | 108             | 1                            | O2                         | 4                              | 4,2%                             | 92                     |
| HAU               | 108             | 1                            | O2                         | 6                              | 6,3%                             | 123                    |
| HK102             | 95              | 1                            | L12(1)                     | 0                              | 0,0%                             | 9                      |
| H20C3K            | 108             | 1                            | L12(2)                     | 3                              | 3,2%                             | 125                    |
| CHEB              | 108             | 1                            | O2                         | 7                              | 7,4%                             | 5                      |
| HK134             | 95              | 1                            | L15(2)                     | 0                              | 0,0%                             | 10                     |
| TEL9              | 108             | 1                            | O2                         | 9                              | 9,5%                             | 73                     |

Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| TR1.32            | 103             | 1                            | O2                         | 3                              | 3,2%                             | 92                     |
| RF-KES1           | 97              | 1                            | A20                        | 4                              | 4,2%                             | 121                    |
| WES               | 108             | 1                            | L5                         | 10                             | 10,5%                            | 61                     |
| DILp1             | 95              | 1                            | O4                         | 1                              | 1,1%                             | 70                     |
| SA-4B             | 107             | 1                            | L12(2)                     | 8                              | 8,4%                             | 120                    |
| HK101             | 95              | 1                            | L15(1)                     | 0                              | 0,0%                             | 9                      |
| TR1.23            | 108             | 1                            | O2                         | 5                              | 5,3%                             | 92                     |
| HF2-1/17          | 108             | 1                            | A30                        | 0                              | 0,0%                             | 4                      |
| 2E7               | 108             | 1                            | A30                        | 1                              | 1,1%                             | 62                     |
| 33.C9             | 107             | 1                            | L12(2)                     | 7                              | 7,4%                             | 126                    |
| 3D6               | 105             | 1                            | L12(2)                     | 2                              | 2,1%                             | 34                     |
| I-2a              | 108             | 1                            | L8                         | 8                              | 8,4%                             | 70                     |
| RF-KL1            | 97              | 1                            | L8                         | 4                              | 4,2%                             | 121                    |
| TNF-E7            | 108             | 1                            | A30                        | 9                              | 9,5%                             | 41                     |
| TR1.22            | 108             | 1                            | O2                         | 7                              | 7,4%                             | 92                     |
| HIV-B35           | 106             | 1                            | O2                         | 2                              | 2,2%                             | 8                      |
| HIV-b22           | 106             | 1                            | O2                         | 2                              | 2,2%                             | 8                      |
| HIV-b27           | 106             | 1                            | O2                         | 2                              | 2,2%                             | 8                      |
| HIV-B8            | 107             | 1                            | O2                         | 10                             | 10,8%                            | 8                      |
| HIV-b8            | 107             | 1                            | O2                         | 10                             | 10,8%                            | 8                      |
| RF-SJ5            | 95              | 1                            | A30                        | 5                              | 5,3%                             | 113                    |
| GAL(I)            | 108             | 1                            | A30                        | 6                              | 6,3%                             | 64                     |
| R3.5H5G           | 108             | 1                            | O2                         | 6                              | 6,3%                             | 70                     |
| HIV-b14           | 106             | 1                            | A20                        | 2                              | 2,2%                             | 8                      |
| TNF-E1            | 105             | 1                            | L5                         | 8                              | 8,4%                             | 41                     |
| WEA               | 108             | 1                            | A30                        | 8                              | 8,4%                             | 37                     |
| EU                | 108             | 1                            | L12(2)                     | 5                              | 5,3%                             | 40                     |
| FOG1-G8           | 108             | 1                            | L8                         | 11                             | 11,6%                            | 41                     |
| 1X7RG1            | 108             | 1                            | L1                         | 8                              | 8,4%                             | 70                     |
| BLI               | 108             | 1                            | L8                         | 3                              | 3,2%                             | 72                     |
| KUE               | 108             | 1                            | L12(2)                     | 11                             | 11,6%                            | 32                     |
| LUNm01            | 108             | 1                            | L12(2)                     | 10                             | 10,5%                            | 6                      |
| HIV-b1            | 106             | 1                            | A20                        | 4                              | 4,3%                             | 8                      |
| HIV-s4            | 103             | 1                            | O2                         | 2                              | 2,2%                             | 8                      |

Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| CAR               | 107             | 1                            | L12(2)                     | 11                             | 11,7%                            | 79                     |
| BR                | 107             | 1                            | L12(2)                     | 11                             | 11,6%                            | 50                     |
| CLL PATIENT 10    | 88              | 1                            | O2                         | 0                              | 0,0%                             | 122                    |
| CLL PATIENT 12    | 88              | 1                            | O2                         | 0                              | 0,0%                             | 122                    |
| KING              | 108             | 1                            | L12(2)                     | 12                             | 12,6%                            | 30                     |
| V13               | 95              | 1                            | L24                        | 0                              | 0,0%                             | 46                     |
| CLL PATIENT 11    | 87              | 1                            | O2                         | 0                              | 0,0%                             | 122                    |
| CLL PATIENT 13    | 87              | 1                            | O2                         | 0                              | 0,0%                             | 122                    |
| CLL PATIENT 9     | 88              | 1                            | O12                        | 1                              | 1,1%                             | 122                    |
| HIV-B2            | 106             | 1                            | A20                        | 9                              | 9,7%                             | 8                      |
| HIV-b2            | 106             | 1                            | A20                        | 9                              | 9,7%                             | 8                      |
| CLL PATIENT 5     | 88              | 1                            | A20                        | 1                              | 1,1%                             | 122                    |
| CLL PATIENT 1     | 88              | 1                            | L8                         | 2                              | 2,3%                             | 122                    |
| CLL PATIENT 2     | 88              | 1                            | L8                         | 0                              | 0,0%                             | 122                    |
| CLL PATIENT 7     | 88              | 1                            | L5                         | 0                              | 0,0%                             | 122                    |
| CLL PATIENT 8     | 88              | 1                            | L5                         | 0                              | 0,0%                             | 122                    |
| HIV-b5            | 105             | 1                            | L5                         | 11                             | 12,0%                            | 8                      |
| CLL PATIENT 3     | 87              | 1                            | L8                         | 1                              | 1,1%                             | 122                    |
| CLL PATIENT 4     | 88              | 1                            | L9                         | 0                              | 0,0%                             | 122                    |
| CLL PATIENT 18    | 85              | 1                            | L9                         | 6                              | 7,1%                             | 122                    |
| CLL PATIENT 17    | 86              | 1                            | L12(2)                     | 7                              | 8,1%                             | 122                    |
| HIV-b20           | 107             | 3                            | A27                        | 11                             | 11,7%                            | 8                      |
| 2C12              | 108             | 1                            | L12(2)                     | 20                             | 21,1%                            | 68                     |
| 1B11              | 108             | 1                            | L12(2)                     | 20                             | 21,1%                            | 68                     |
| 1H1               | 108             | 1                            | L12(2)                     | 21                             | 22,1%                            | 68                     |
| 2A12              | 108             | 1                            | L12(2)                     | 21                             | 22,1%                            | 68                     |
| CUR               | 109             | 3                            | A27                        | 0                              | 0,0%                             | 66                     |
| GLO               | 109             | 3                            | A27                        | 0                              | 0,0%                             | 16                     |
| RF-TS1            | 96              | 3                            | A27                        | 0                              | 0,0%                             | 121                    |
| GAR'              | 109             | 3                            | A27                        | 0                              | 0,0%                             | 67                     |
| FLO               | 109             | 3                            | A27                        | 0                              | 0,0%                             | 66                     |
| PIE               | 109             | 3                            | A27                        | 0                              | 0,0%                             | 91                     |
| HAH 14.1          | 109             | 3                            | A27                        | 1                              | 1,0%                             | 51                     |
| HAH 14.2          | 109             | 3                            | A27                        | 1                              | 1,0%                             | 51                     |

Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| HAH 16.1          | 109             | 3                            | A27                        | 1                              | 1,0%                             | 51                     |
| NOV               | 109             | 3                            | A27                        | 1                              | 1,0%                             | 52                     |
| 33.F12            | 108             | 3                            | A27                        | 1                              | 1,0%                             | 126                    |
| 8E10              | 110             | 3                            | A27                        | 1                              | 1,0%                             | 25                     |
| TH3               | 109             | 3                            | A27                        | 1                              | 1,0%                             | 25                     |
| HIC (R)           | 108             | 3                            | A27                        | 0                              | 0,0%                             | 51                     |
| SON               | 110             | 3                            | A27                        | 1                              | 1,0%                             | 67                     |
| PAY               | 109             | 3                            | A27                        | 1                              | 1,0%                             | 66                     |
| GOT               | 109             | 3                            | A27                        | 1                              | 1,0%                             | 67                     |
| mAbA6H4C5         | 109             | 3                            | A27                        | 1                              | 1,0%                             | 12                     |
| BOR'              | 109             | 3                            | A27                        | 2                              | 2,1%                             | 84                     |
| RF-SJ3            | 96              | 3                            | A27                        | 2                              | 2,1%                             | 121                    |
| SIE               | 109             | 3                            | A27                        | 2                              | 2,1%                             | 15                     |
| ESC               | 109             | 3                            | A27                        | 2                              | 2,1%                             | 98                     |
| HEW'              | 110             | 3                            | A27                        | 2                              | 2,1%                             | 98                     |
| YES8c             | 109             | 3                            | A27                        | 3                              | 3,1%                             | 33                     |
| TI                | 109             | 3                            | A27                        | 3                              | 3,1%                             | 114                    |
| mAb113            | 109             | 3                            | A27                        | 3                              | 3,1%                             | 71                     |
| HEW               | 107             | 3                            | A27                        | 0                              | 0,0%                             | 94                     |
| BRO               | 106             | 3                            | A27                        | 0                              | 0,0%                             | 94                     |
| ROB               | 106             | 3                            | A27                        | 0                              | 0,0%                             | 94                     |
| NG9               | 96              | 3                            | A27                        | 4                              | 4,2%                             | 11                     |
| NEU               | 109             | 3                            | A27                        | 4                              | 4,2%                             | 66                     |
| WOL               | 109             | 3                            | A27                        | 4                              | 4,2%                             | 2                      |
| 35G6              | 109             | 3                            | A27                        | 4                              | 4,2%                             | 59                     |
| RF-SJ4            | 109             | 3                            | A11                        | 0                              | 0,0%                             | 88                     |
| KAS               | 109             | 3                            | A27                        | 4                              | 4,2%                             | 84                     |
| BRA               | 106             | 3                            | A27                        | 1                              | 1,1%                             | 94                     |
| HAH               | 106             | 3                            | A27                        | 1                              | 1,1%                             | 94                     |
| HIC               | 105             | 3                            | A27                        | 0                              | 0,0%                             | 94                     |
| FS-2              | 109             | 3                            | A27                        | 6                              | 6,3%                             | 87                     |
| JH'               | 107             | 3                            | A27                        | 6                              | 6,3%                             | 38                     |
| EV1-15            | 109             | 3                            | A27                        | 6                              | 6,3%                             | 83                     |
| SCA               | 108             | 3                            | A27                        | 6                              | 6,3%                             | 65                     |

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Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| mAb112            | 109             | 3                            | A27                        | 6                              | 6,3%                             | 71                     |
| SIC               | 103             | 3                            | A27                        | 3                              | 3,3%                             | 94                     |
| SA-4A             | 109             | 3                            | A27                        | 6                              | 6,3%                             | 120                    |
| SER               | 108             | 3                            | A27                        | 6                              | 6,3%                             | 98                     |
| GOL               | 109             | 3                            | A27                        | 7                              | 7,3%                             | 82                     |
| B5G10K            | 105             | 3                            | A27                        | 9                              | 9,7%                             | 125                    |
| HG2B10K           | 110             | 3                            | A27                        | -9                             | 9,4%                             | 125                    |
| Taykv322          | 105             | 3                            | A27                        | 5                              | 5,4%                             | 52                     |
| CLL PATIENT 24    | 89              | 3                            | A27                        | 1                              | 1,1%                             | 122                    |
| HIV-b24           | 107             | 3                            | A27                        | 7                              | 7,4%                             | 8                      |
| HIV-b6            | 107             | 3                            | A27                        | 7                              | 7,4%                             | 8                      |
| Taykv310          | 99              | 3                            | A27                        | 1                              | 1,1%                             | 52                     |
| KA3D1             | 108             | 3                            | L6                         | 0                              | 0,0%                             | 85                     |
| 19.E7             | 107             | 3                            | L6                         | 0                              | 0,0%                             | 126                    |
| rsv6L             | 109             | 3                            | A27                        | 12                             | 12,5%                            | 7                      |
| Taykv320          | 98              | 3                            | A27                        | 1                              | 1,2%                             | 52                     |
| Vh                | 96              | 3                            | L10(2)                     | 0                              | 0,0%                             | 89                     |
| LS8               | 108             | 3                            | L6                         | 1                              | 1,1%                             | 109                    |
| LS1               | 108             | 3                            | L6                         | 1                              | 1,1%                             | 109                    |
| LS2S3-3           | 107             | 3                            | L6                         | 2                              | 2,1%                             | 99                     |
| LS2               | 108             | 3                            | L6                         | 1                              | 1,1%                             | 109                    |
| LS7               | 108             | 3                            | L6                         | 1                              | 1,1%                             | 109                    |
| LS2S3-4d          | 107             | 3                            | L6                         | 2                              | 2,1%                             | 99                     |
| LS2S3-4a          | 107             | 3                            | L6                         | 2                              | 2,1%                             | 99                     |
| LS4               | 108             | 3                            | L6                         | 1                              | 1,1%                             | 109                    |
| LS6               | 108             | 3                            | L6                         | 1                              | 1,1%                             | 109                    |
| LS2S3-10a         | 107             | 3                            | L6                         | 2                              | 2,1%                             | 99                     |
| LS2S3-8c          | 107             | 3                            | L6                         | 2                              | 2,1%                             | 99                     |
| LS5               | 108             | 3                            | L6                         | 1                              | 1,1%                             | 109                    |
| LS2S3-5           | 107             | 3                            | L6                         | 3                              | 3,2%                             | 99                     |
| LUNm03            | 109             | 3                            | A27                        | 13                             | 13,5%                            | 6                      |
| IARC/BL41         | 108             | 3                            | A27                        | 13                             | 13,7%                            | 55                     |
| slkv22            | 99              | 3                            | A27                        | 3                              | 3,5%                             | 13                     |
| POP               | 108             | 3                            | L6                         | 4                              | 4,2%                             | 111                    |

Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| LS2S3-10b         | 107             | 3                            | L6                         | 3                              | 3,2%                             | 99                     |
| LS2S3-8f          | 107             | 3                            | L6                         | 3                              | 3,2%                             | 99                     |
| LS2S3-12          | 107             | 3                            | L6                         | 3                              | 3,2%                             | 99                     |
| HIV-B30           | 107             | 3                            | A27                        | 11                             | 11,7%                            | 8                      |
| HIV-B20           | 107             | 3                            | A27                        | 11                             | 11,7%                            | 8                      |
| HIV-b3            | 108             | 3                            | A27                        | 11                             | 11,7%                            | 8                      |
| HIV-s6            | 104             | 3                            | A27                        | 9                              | 9,9%                             | 8                      |
| YSE               | 107             | 3                            | L2/L16                     | 1                              | 1,1%                             | 72                     |
| POM               | 109             | 3                            | L2/L16                     | 9                              | 9,4%                             | 53                     |
| Humkv328          | 95              | 3                            | L2/L16                     | 1                              | 1,1%                             | 19                     |
| CLL               | 109             | 3                            | L2/L16                     | 3                              | 3,2%                             | 47                     |
| LES               | 96              | 3                            | L2/L16                     | 3                              | 3,2%                             | 38                     |
| HIV-s5            | 104             | 3                            | A27                        | 11                             | 12,1%                            | 8                      |
| HIV-s7            | 104             | 3                            | A27                        | 11                             | 12,1%                            | 8                      |
| slkv1             | 99              | 3                            | A27                        | 7                              | 8,1%                             | 13                     |
| Humka31es         | 95              | 3                            | L2/L16                     | 4                              | 4,2%                             | 18                     |
| slkv12            | 101             | 3                            | A27                        | 8                              | 9,2%                             | 13                     |
| RF-TS2            | 95              | 3                            | L2/L16                     | 3                              | 3,2%                             | 121                    |
| II-1              | 109             | 3                            | L2/L16                     | 4                              | 4,2%                             | 70                     |
| HIV-s3            | 105             | 3                            | A27                        | 13                             | 14,3%                            | 8                      |
| RF-TMC1           | 96              | 3                            | L6                         | 10                             | 10,5%                            | 121                    |
| GER               | 109             | 3                            | L2/L16                     | 7                              | 7,4%                             | 75                     |
| GF4/1.1           | 109             | 3                            | L2/L16                     | 8                              | 8,4%                             | 36                     |
| mAb114            | 109             | 3                            | L2/L16                     | 6                              | 6,3%                             | 71                     |
| HIV-loop13        | 109             | 3                            | L2/L16                     | 7                              | 7,4%                             | 8                      |
| bkv16             | 86              | 3                            | L6                         | 1                              | 1,2%                             | 13                     |
| CLL PATIENT 29    | 86              | 3                            | L6                         | 1                              | 1,2%                             | 122                    |
| slkv9             | 98              | 3                            | L6                         | 3                              | 3,5%                             | 13                     |
| bkv17             | 99              | 3                            | L6                         | 1                              | 1,2%                             | 13                     |
| slkv14            | 99              | 3                            | L6                         | 1                              | 1,2%                             | 13                     |
| slkv16            | 101             | 3                            | L6                         | 2                              | 2,3%                             | 13                     |
| bkv33             | 101             | 3                            | L6                         | 4                              | 4,7%                             | 13                     |
| slkv15            | 99              | 3                            | L6                         | 2                              | 2,3%                             | 13                     |
| bkv6              | 100             | 3                            | L6                         | 3                              | 3,5%                             | 13                     |



Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| R6B8K             | 108             | 3                            | L2/L16                     | 12                             | 12,6%                            | 125                    |
| AL 700            | 107             | 3                            | L2/L16                     | 9                              | 9,5%                             | 117                    |
| slkv11            | 100             | 3                            | L2/L16                     | 3                              | 3,5%                             | 13                     |
| slkv4             | 97              | 3                            | L6                         | 4                              | 4,8%                             | 13                     |
| CLL PATIENT 26    | 87              | 3                            | L2/L16                     | 1                              | 1,1%                             | 122                    |
| AL Se124          | 103             | 3                            | L2/L16                     | 9                              | 9,5%                             | 117                    |
| slkv13            | 100             | 3                            | L2/L16                     | 6                              | 7,0%                             | 13                     |
| bkv7              | 100             | 3                            | L2/L16                     | 5                              | 5,8%                             | 13                     |
| bkv22             | 100             | 3                            | L2/L16                     | 6                              | 7,0%                             | 13                     |
| CLL PATIENT 27    | 84              | 3                            | L2/L16                     | 0                              | 0,0%                             | 122                    |
| bkv35             | 100             | 3                            | L6                         | 8                              | 9,3%                             | 13                     |
| CLL PATIENT 25    | 87              | 3                            | L2/L16                     | 4                              | 4,6%                             | 122                    |
| slkv3             | 86              | 3                            | L2/L16                     | 7                              | 8,1%                             | 13                     |
| slkv7             | 99              | 1                            | O2                         | 7                              | 8,1%                             | 13                     |
| HuFd79            | 111             | 3                            | L2/L16                     | 24                             | 24,2%                            | 21                     |
| RAD               | 99              | 3                            | A27                        | 9                              | 10,3%                            | 78                     |
| CLL PATIENT 28    | 83              | 3                            | L2/L16                     | 4                              | 4,8%                             | 122                    |
| REE               | 104             | 3                            | L2/L16                     | 25                             | 27,2%                            | 95                     |
| FR4               | 99              | 3                            | A27                        | 8                              | 9,2%                             | 77                     |
| MD3.3             | 92              | 3                            | L6                         | 1                              | 1,3%                             | 54                     |
| MD3.1             | 92              | 3                            | L6                         | 0                              | 0,0%                             | 54                     |
| GA3.6             | 92              | 3                            | L6                         | 2                              | 2,6%                             | 54                     |
| M3.5N             | 92              | 3                            | L6                         | 3                              | 3,8%                             | 54                     |
| WEI'              | 82              | 3                            | A27                        | 0                              | 0,0%                             | 65                     |
| MD3.4             | 92              | 3                            | L2/L16                     | 1                              | 1,3%                             | 54                     |
| MD3.2             | 91              | 3                            | L6                         | 3                              | 3,8%                             | 54                     |
| VER               | 97              | 3                            | A27                        | 19                             | 22,4%                            | 20                     |
| CLL PATIENT 30    | 78              | 3                            | L6                         | 3                              | 3,8%                             | 122                    |
| M3.1N             | 92              | 3                            | L2/L16                     | 1                              | 1,3%                             | 54                     |
| MD3.6             | 91              | 3                            | L2/L16                     | 0                              | 0,0%                             | 54                     |
| MD3.8             | 91              | 3                            | L2/L16                     | 0                              | 0,0%                             | 54                     |
| GA3.4             | 92              | 3                            | L6                         | 7                              | 9,0%                             | 54                     |
| M3.6N             | 92              | 3                            | A27                        | 0                              | 0,0%                             | 54                     |
| MD3.10            | 92              | 3                            | A27                        | 0                              | 0,0%                             | 54                     |

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Table 2A: (continued)

| Name <sup>1</sup>   | aa <sup>2</sup> | Computed<br>family <sup>3</sup> | Germline<br>gene <sup>4</sup> | Diff. to<br>germline <sup>5</sup> | % diff. to<br>germline <sup>6</sup> | Reference <sup>7</sup> |
|---------------------|-----------------|---------------------------------|-------------------------------|-----------------------------------|-------------------------------------|------------------------|
| MD3.13              | 91              | 3                               | A27                           | 0                                 | 0,0%                                | 54                     |
| MD3.7               | 93              | 3                               | A27                           | 0                                 | 0,0%                                | 54                     |
| MD3.9               | 93              | 3                               | A27                           | 0                                 | 0,0%                                | 54                     |
| GA3.1               | 93              | 3                               | A27                           | 6                                 | 7,6%                                | 54                     |
| bkv32               | 101             | 3                               | A27                           | 5                                 | 5,7%                                | 13                     |
| GA3.5               | 93              | 3                               | A27                           | 5                                 | 6,3%                                | 54                     |
| GA3.7               | 92              | 3                               | A27                           | 7                                 | 8,9%                                | 54                     |
| MD3.12              | 92              | 3                               | A27                           | 2                                 | 2,5%                                | 54                     |
| M3.2N               | 90              | 3                               | L6                            | 6                                 | 7,8%                                | 54                     |
| MD3.5               | 92              | 3                               | A27                           | 1                                 | 1,3%                                | 54                     |
| M3.4N               | 91              | 3                               | L2/L16                        | 8                                 | 10,3%                               | 54                     |
| M3.8N               | 91              | 3                               | L2/L16                        | 7                                 | 9,0%                                | 54                     |
| M3.7N               | 92              | 3                               | A27                           | 3                                 | 3,8%                                | 54                     |
| GA3.2               | 92              | 3                               | A27                           | 9                                 | 11,4%                               | 54                     |
| GA3.8               | 93              | 3                               | A27                           | 4                                 | 5,1%                                | 54                     |
| GA3.3               | 92              | 3                               | A27                           | 8                                 | 10,1%                               | 54                     |
| M3.3N               | 92              | 3                               | A27                           | 5                                 | 6,3%                                | 54                     |
| B6                  | 83              | 3                               | A27                           | 8                                 | 11,3%                               | 78                     |
| E29.1 KAPPA         | 78              | 3                               | L2/L16                        | 0                                 | 0,0%                                | 22                     |
| SCW                 | 108             | 1                               | O8                            | 12                                | 12,6%                               | 31                     |
| REI-based CAMPATH-9 | 107             | 1                               | O8                            | 14                                | 14,7%                               | 39                     |
| RZ                  | 107             | 1                               | O8                            | 14                                | 14,7%                               | 50                     |
| BI                  | 108             | 1                               | O8                            | 14                                | 14,7%                               | 14                     |
| AND                 | 107             | 1                               | O2                            | 13                                | 13,7%                               | 69                     |
| 2A4                 | 109             | 1                               | O2                            | 12                                | 12,6%                               | 23                     |
| KA                  | 108             | 1                               | O8                            | 19                                | 20,0%                               | 107                    |
| MEV                 | 109             | 1                               | O2                            | 14                                | 14,7%                               | 29                     |
| DEE                 | 106             | 1                               | O2                            | 13                                | 14,0%                               | 76                     |
| OU(I0C)             | 108             | 1                               | O2                            | 18                                | 18,9%                               | 60                     |
| HuRSV19VK           | 111             | 1                               | O8                            | 21                                | 21,0%                               | 115                    |
| SP2                 | 108             | 1                               | O2                            | 17                                | 17,9%                               | 93                     |
| BJ26                | 99              | 1                               | O8                            | 21                                | 24,1%                               | 1                      |
| NI                  | 112             | 1                               | O8                            | 24                                | 24,2%                               | 106                    |
| BMA 0310EUCIV2      | 106             | 1                               | L12(1)                        | 21                                | 22,3%                               | 105                    |

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Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| CLL PATIENT 6     | 71              | 1                            | A20                        | 0                              | 0,0%                             | 122                    |
| BJ19              | 85              | 1                            | O8                         | 16                             | 21,9%                            | 1                      |
| GM 607            | 113             | 2                            | A3                         | 0                              | 0,0%                             | 58                     |
| R5A3K             | 114             | 2                            | A3                         | 1                              | 1,0%                             | 125                    |
| R1C8K             | 114             | 2                            | A3                         | 1                              | 1,0%                             | 125                    |
| VK2.R149          | 113             | 2                            | A3                         | 2                              | 2,0%                             | 118                    |
| TR1.6             | 109             | 2                            | A3                         | 4                              | 4,0%                             | 92                     |
| TR1.37            | 104             | 2                            | A3                         | 5                              | 5,0%                             | 92                     |
| FS-1              | 113             | 2                            | A3                         | 6                              | 6,0%                             | 87                     |
| TR1.8             | 110             | 2                            | A3                         | 6                              | 6,0%                             | 92                     |
| NIM               | 113             | 2                            | A3                         | 8                              | 8,0%                             | 28                     |
| Inc               | 112             | 2                            | A3                         | 11                             | 11,0%                            | 35                     |
| TEW               | 107             | 2                            | A3                         | 6                              | 6,4%                             | 96                     |
| CUM               | 114             | 2                            | O1                         | 7                              | 6,9%                             | 44                     |
| HRF1              | 71              | 2                            | A3                         | 4                              | 5,6%                             | 124                    |
| CLL PATIENT 19    | 87              | 2                            | A3                         | 0                              | 0,0%                             | 122                    |
| CLL PATIENT 20    | 87              | 2                            | A3                         | 0                              | 0,0%                             | 122                    |
| MIL               | 112             | 2                            | A3                         | 16                             | 16,2%                            | 26                     |
| FR                | 113             | 2                            | A3                         | 20                             | 20,0%                            | 101                    |
| MAL-Urine         | 83              | 1                            | O2                         | 6                              | 8,6%                             | 102                    |
| Taykv306          | 73              | 3                            | A27                        | 1                              | 1,6%                             | 52                     |
| Taykv312          | 75              | 3                            | A27                        | 1                              | 1,6%                             | 52                     |
| HIV-b29           | 93              | 3                            | A27                        | 14                             | 17,5%                            | 8                      |
| 1-185-37          | 110             | 3                            | A27                        | 0                              | 0,0%                             | 119                    |
| 1-187-29          | 110             | 3                            | A27                        | 0                              | 0,0%                             | 119                    |
| TT117             | 110             | 3                            | A27                        | 9                              | 9,4%                             | 63                     |
| HIV-loop8         | 108             | 3                            | A27                        | 16                             | 16,8%                            | 8                      |
| rsv23L            | 108             | 3                            | A27                        | 16                             | 16,8%                            | 7                      |
| HIV-b7            | 107             | 3                            | A27                        | 14                             | 14,9%                            | 8                      |
| HIV-b11           | 107             | 3                            | A27                        | 15                             | 16,0%                            | 8                      |
| HIV-LC1           | 107             | 3                            | A27                        | 19                             | 20,2%                            | 8                      |
| HIV-LC7           | 107             | 3                            | A27                        | 20                             | 21,3%                            | 8                      |
| HIV-LC22          | 107             | 3                            | A27                        | 21                             | 22,3%                            | 8                      |
| HIV-LC13          | 107             | 3                            | A27                        | 21                             | 22,3%                            | 8                      |

Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| HIV-LC3           | 107             | 3                            | A27                        | 21                             | 22,3%                            | 8                      |
| HIV-LC5           | 107             | 3                            | A27                        | 21                             | 22,3%                            | 8                      |
| HIV-LC28          | 107             | 3                            | A27                        | 21                             | 22,3%                            | 8                      |
| HIV-b4            | 107             | 3                            | A27                        | 22                             | 23,4%                            | 8                      |
| CLL PATIENT 31    | 87              | 3                            | A27                        | 15                             | 17,2%                            | 122                    |
| HIV-loop2         | 108             | 3                            | L2/L16                     | 17                             | 17,9%                            | 8                      |
| HIV-loop35        | 108             | 3                            | L2/L16                     | 17                             | 17,9%                            | 8                      |
| HIV-LC11          | 107             | 3                            | A27                        | 23                             | 24,5%                            | 8                      |
| HIV-LC24          | 107             | 3                            | A27                        | 23                             | 24,5%                            | 8                      |
| HIV-b12           | 107             | 3                            | A27                        | 24                             | 25,5%                            | 8                      |
| HIV-LC25          | 107             | 3                            | A27                        | 24                             | 25,5%                            | 8                      |
| HIV-b21           | 107             | 3                            | A27                        | 24                             | 25,5%                            | 8                      |
| HIV-LC26          | 107             | 3                            | A27                        | 26                             | 27,7%                            | 8                      |
| G3D10K            | 108             | 1                            | L12(2)                     | 12                             | 12,6%                            | 125                    |
| TT125             | 108             | 1                            | L5                         | 8                              | 8,4%                             | 63                     |
| HIV-s2            | 103             | 3                            | A27                        | 28                             | 31,1%                            | 8                      |
| 265-695           | 108             | 1                            | L5                         | 7                              | 7,4%                             | 3                      |
| 2-115-19          | 108             | 1                            | A30                        | 2                              | 2,1%                             | 119                    |
| rsv13L            | 107             | 1                            | O2                         | 20                             | 21,1%                            | 7                      |
| HIV-b18           | 106             | 1                            | O2                         | 14                             | 15,1%                            | 8                      |
| RF-KL5            | 98              | 3                            | L6                         | 36                             | 36,7%                            | 97                     |
| ZM1-1             | 113             | 2                            | A17                        | 7                              | 7,0%                             | 3                      |
| HIV-s8            | 103             | 1                            | O8                         | 16                             | 17,8%                            | 8                      |
| K- EV15           | 95              | 5                            | B2                         | 0                              | 0,0%                             | 112                    |
| RF-TS3            | 100             | 2                            | A23                        | 0                              | 0,0%                             | 121                    |
| HF-21/28          | 111             | 2                            | A17                        | 1                              | 1,0%                             | 17                     |
| RPMI6410          | 113             | 2                            | A17                        | 1                              | 1,0%                             | 42                     |
| JC11              | 113             | 2                            | A17                        | 1                              | 1,0%                             | 49                     |
| O-81              | 114             | 2                            | A17                        | 5                              | 5,0%                             | 45                     |
| FK-001            | 113             | 4                            | B3                         | 0                              | 0,0%                             | 81                     |
| CD5+.28           | 101             | 4                            | B3                         | 1                              | 1,0%                             | 27                     |
| LEN               | 114             | 4                            | B3                         | 1                              | 1,0%                             | 104                    |
| UC                | 114             | 4                            | B3                         | 1                              | 1,0%                             | 111                    |
| CD5+.5            | 101             | 4                            | B3                         | 1                              | 1,0%                             | 27                     |

Table 2A: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>5</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| CD5+.26           | 101             | 4                            | B3                         | 1                              | 1,0%                             | 27                     |
| CD5+.12           | 101             | 4                            | B3                         | 2                              | 2,0%                             | 27                     |
| CD5+.23           | 101             | 4                            | B3                         | 2                              | 2,0%                             | 27                     |
| CD5+.7            | 101             | 4                            | B3                         | 2                              | 2,0%                             | 27                     |
| VJI               | 113             | 4                            | B3                         | 3                              | 3,0%                             | 56                     |
| LOC               | 113             | 4                            | B3                         | 3                              | 3,0%                             | 72                     |
| MAL               | 113             | 4                            | B3                         | 3                              | 3,0%                             | 72                     |
| CD5+.6            | 101             | 4                            | B3                         | 3                              | 3,0%                             | 27                     |
| H2F               | 113             | 4                            | B3                         | 3                              | 3,0%                             | 70                     |
| PB17IV            | 114             | 4                            | B3                         | 4                              | 4,0%                             | 74                     |
| CD5+.27           | 101             | 4                            | B3                         | 4                              | 4,0%                             | 27                     |
| CD5+.9            | 101             | 4                            | B3                         | 4                              | 4,0%                             | 27                     |
| CD5-.28           | 101             | 4                            | B3                         | 5                              | 5,0%                             | 27                     |
| CD5-.26           | 101             | 4                            | B3                         | 6                              | 5,9%                             | 27                     |
| CD5+.24           | 101             | 4                            | B3                         | 6                              | 5,9%                             | 27                     |
| CD5+.10           | 101             | 4                            | B3                         | 6                              | 5,9%                             | 27                     |
| CD5-.19           | 101             | 4                            | B3                         | 6                              | 5,9%                             | 27                     |
| CD5-.18           | 101             | 4                            | B3                         | 7                              | 6,9%                             | 27                     |
| CD5-.16           | 101             | 4                            | B3                         | 8                              | 7,9%                             | 27                     |
| CD5-.24           | 101             | 4                            | B3                         | 8                              | 7,9%                             | 27                     |
| CD5-.17           | 101             | 4                            | B3                         | 10                             | 9,9%                             | 27                     |
| MD4.1             | 92              | 4                            | B3                         | 0                              | 0,0%                             | 54                     |
| MD4.4             | 92              | 4                            | B3                         | 0                              | 0,0%                             | 54                     |
| MD4.5             | 92              | 4                            | B3                         | 0                              | 0,0%                             | 54                     |
| MD4.6             | 92              | 4                            | B3                         | 0                              | 0,0%                             | 54                     |
| MD4.7             | 92              | 4                            | B3                         | 0                              | 0,0%                             | 54                     |
| MD4.2             | 92              | 4                            | B3                         | 1                              | 1,3%                             | 54                     |
| MD4.3             | 92              | 4                            | B3                         | 5                              | 6,3%                             | 54                     |
| CLL PATIENT 22    | 87              | 2                            | A17                        | 2                              | 2,3%                             | 122                    |
| CLL PATIENT 23    | 84              | 2                            | A17                        | 2                              | 2,4%                             | 122                    |

Table 2B: rearranged human lambda sequences

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| WAH               | 110             | 1                            | DPL3                       | 7                              | 7%                               | 68                     |
| 1B9/F2            | 112             | 1                            | DPL3                       | 7                              | 7%                               | 9                      |
| DIA               | 112             | 1                            | DPL2                       | 7                              | 7%                               | 36                     |
| mAb67             | 89              | 1                            | DPL3                       | 0                              | 0%                               | 29                     |
| HiH2              | 110             | 1                            | DPL3                       | 12                             | 11%                              | 3                      |
| NIG-77            | 112             | 1                            | DPL2                       | 9                              | 9%                               | 72                     |
| OKA               | 112             | 1                            | DPL2                       | 7                              | 7%                               | 84                     |
| KOL               | 112             | 1                            | DPL2                       | 12                             | 11%                              | 40                     |
| T2:C5             | 111             | 1                            | DPL5                       | 0                              | 0%                               | 6                      |
| T2:C14            | 110             | 1                            | DPL5                       | 0                              | 0%                               | 6                      |
| PR-TS1            | 110             | 1                            | DPL5                       | 0                              | 0%                               | 55                     |
| 4G12              | 111             | 1                            | DPL5                       | 1                              | 1%                               | 35                     |
| KIM46L            | 112             | 1                            | HUMLV117                   | 0                              | 0%                               | 8                      |
| Fog-B             | 111             | 1                            | DPL5                       | 3                              | 3%                               | 31                     |
| 9F2L              | 111             | 1                            | DPL5                       | 3                              | 3%                               | 79                     |
| mAb111            | 110             | 1                            | DPL5                       | 3                              | 3%                               | 48                     |
| PHOX15            | 111             | 1                            | DPL5                       | 4                              | 4%                               | 49                     |
| BL2               | 111             | 1                            | DPL5                       | 4                              | 4%                               | 74                     |
| NIG-64            | 111             | 1                            | DPL5                       | 4                              | 4%                               | 72                     |
| RF-SJ2            | 100             | 1                            | DPL5                       | 6                              | 6%                               | 78                     |
| AL EZI            | 112             | 1                            | DPL5                       | 7                              | 7%                               | 41                     |
| ZIM               | 112             | 1                            | HUMLV117                   | 7                              | 7%                               | 18                     |
| RF-SJ1            | 100             | 1                            | DPL5                       | 9                              | 9%                               | 78                     |
| IGLV1.1           | 98              | 1                            | DPL4                       | 0                              | 0%                               | 1                      |
| NEW               | 112             | 1                            | HUMLV117                   | 11                             | 10%                              | 42                     |
| CB-201            | 87              | 1                            | DPL2                       | 1                              | 1%                               | 62                     |
| MEM               | 109             | 1                            | DPL2                       | 6                              | 6%                               | 50                     |
| H210              | 111             | 2                            | DPL10                      | 4                              | 4%                               | 45                     |
| NOV               | 110             | 2                            | DPL10                      | 8                              | 8%                               | 25                     |
| NEI               | 111             | 2                            | DPL10                      | 8                              | 8%                               | 24                     |
| AL MC             | 110             | 2                            | DPL11                      | 6                              | 6%                               | 28                     |
| MES               | 112             | 2                            | DPL11                      | 8                              | 8%                               | 84                     |
| FOG1-A3           | 111             | 2                            | DPL11                      | 9                              | 9%                               | 27                     |
| AL NOV            | 112             | 2                            | DPL11                      | 7                              | 7%                               | 28                     |

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Table 2B: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| HMST-1            | 110             | 2                            | DPL11                      | 4                              | 4%                               | 82                     |
| HBW4-1            | 108             | 2                            | DPL12                      | 9                              | 9%                               | 52                     |
| WH                | 110             | 2                            | DPL11                      | 11                             | 11%                              | 34                     |
| 11-50             | 110             | 2                            | DPL11                      | 7                              | 7%                               | 82                     |
| HBp2              | 110             | 2                            | DPL12                      | 8                              | 8%                               | 3                      |
| NIG-84            | 113             | 2                            | DPL11                      | 12                             | 11%                              | 73                     |
| VIL               | 112             | 2                            | DPL11                      | 9                              | 9%                               | 58                     |
| TRO               | 111             | 2                            | DPL12                      | 10                             | 10%                              | 61                     |
| ES492             | 108             | 2                            | DPL11                      | 15                             | 15%                              | 76                     |
| mAb216            | 89              | 2                            | DPL12                      | 1                              | 1%                               | 7                      |
| BSA3              | 109             | 3                            | DPL16                      | 0                              | 0%                               | 49                     |
| THY-29            | 110             | 3                            | DPL16                      | 0                              | 0%                               | 27                     |
| PR-TS2            | 108             | 3                            | DPL16                      | 0                              | 0%                               | 55                     |
| E29.1 LAMBDA      | 107             | 3                            | DPL16                      | 1                              | 1%                               | 13                     |
| mAb63             | 109             | 3                            | DPL16                      | 2                              | 2%                               | 29                     |
| TEL14             | 110             | 3                            | DPL16                      | 6                              | 6%                               | 49                     |
| 6H-3C4            | 108             | 3                            | DPL16                      | 7                              | 7%                               | 39                     |
| SH                | 109             | 3                            | DPL16                      | 7                              | 7%                               | 70                     |
| AL GIL            | 109             | 3                            | DPL16                      | 8                              | 8%                               | 23                     |
| H6-3C4            | 108             | 3                            | DPL16                      | 8                              | 8%                               | 83                     |
| V-lambda-2.DS     | 111             | 2                            | DPL11                      | 3                              | 3%                               | 15                     |
| 8.12 ID           | 110             | 2                            | DPL11                      | 3                              | 3%                               | 81                     |
| DSC               | 111             | 2                            | DPL11                      | 3                              | 3%                               | 56                     |
| PV11              | 110             | 2                            | DPL11                      | 1                              | 1%                               | 56                     |
| 33.H11            | 110             | 2                            | DPL11                      | 4                              | 4%                               | 81                     |
| AS17              | 111             | 2                            | DPL11                      | 7                              | 7%                               | 56                     |
| SD6               | 110             | 2                            | DPL11                      | 7                              | 7%                               | 56                     |
| KS3               | 110             | 2                            | DPL11                      | 9                              | 9%                               | 56                     |
| PV6               | 110             | 2                            | DPL12                      | 5                              | 5%                               | 56                     |
| NGD9              | 110             | 2                            | DPL11                      | 7                              | 7%                               | 56                     |
| MUC1-1            | 111             | 2                            | DPL11                      | 11                             | 10%                              | 27                     |
| A30c              | 111             | 2                            | DPL10                      | 6                              | 6%                               | 56                     |
| KS6               | 110             | 2                            | DPL12                      | 6                              | 6%                               | 56                     |
| TEL13             | 111             | 2                            | DPL11                      | 11                             | 10%                              | 49                     |

Table 2B: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| AS7               | 110             | 2                            | DPL12                      | 6                              | 6%                               | 56                     |
| MCG               | 112             | 2                            | DPL12                      | 12                             | 11%                              | 20                     |
| U266L             | 110             | 2                            | DPL12                      | 13                             | 12%                              | 77                     |
| PR-SJ2            | 110             | 2                            | DPL12                      | 14                             | 13%                              | 55                     |
| BOH               | 112             | 2                            | DPL12                      | 11                             | 10%                              | 37                     |
| TOG               | 111             | 2                            | DPL11                      | 19                             | 18%                              | 53                     |
| TEL16             | 111             | 2                            | DPL11                      | 19                             | 18%                              | 49                     |
| No.13             | 110             | 2                            | DPL10                      | 14                             | 13%                              | 52                     |
| BO                | 112             | 2                            | DPL12                      | 18                             | 17%                              | 80                     |
| WIN               | 112             | 2                            | DPL12                      | 17                             | 16%                              | 11                     |
| BUR               | 104             | 2                            | DPL12                      | 15                             | 15%                              | 46                     |
| NIG-58            | 110             | 2                            | DPL12                      | 20                             | 19%                              | 69                     |
| WEIR              | 112             | 2                            | DPL11                      | 26                             | 25%                              | 21                     |
| THY-32            | 111             | 1                            | DPL8                       | 8                              | 8%                               | 27                     |
| TNF-H9G1          | 111             | 1                            | DPL8                       | 9                              | 9%                               | 27                     |
| mAb61             | 111             | 1                            | DPL3                       | 1                              | 1%                               | 29                     |
| LV1L1             | 98              | 1                            | DPL2                       | 0                              | 0%                               | 54                     |
| HA                | 113             | 1                            | DPL3                       | 14                             | 13%                              | 63                     |
| LA1L1             | 111             | 1                            | DPL2                       | 3                              | 3%                               | 54                     |
| RHE               | 112             | 1                            | DPL1                       | 17                             | 16%                              | 22                     |
| K1B12L            | 113             | 1                            | DPL8                       | 17                             | 16%                              | 79                     |
| LOC               | 113             | 1                            | DPL2                       | 15                             | 14%                              | 84                     |
| NIG-51            | 112             | 1                            | DPL2                       | 12                             | 11%                              | 67                     |
| NEWM              | 104             | 1                            | DPL8                       | 23                             | 22%                              | 10                     |
| MD3-4             | 106             | 3                            | DPL23                      | 14                             | 13%                              | 4                      |
| COX               | 112             | 1                            | DPL2                       | 13                             | 12%                              | 84                     |
| HiH10             | 106             | 3                            | DPL23                      | 13                             | 12%                              | 3                      |
| VOR               | 112             | 1                            | DPL2                       | 16                             | 15%                              | 16                     |
| AL POL            | 113             | 1                            | DPL2                       | 16                             | 15%                              | 57                     |
| CD4-74            | 111             | 1                            | DPL2                       | 19                             | 18%                              | 27                     |
| AMYLOID MOL       | 102             | 3                            | DPL23                      | 15                             | 15%                              | 30                     |
| OST577            | 108             | 3                            | Humlv318                   | 10                             | 10%                              | 4                      |
| NIG-48            | 113             | 1                            | DPL3                       | 42                             | 40%                              | 66                     |
| CARR              | 108             | 3                            | DPL23                      | 18                             | 17%                              | 19                     |

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Table 2B: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| mAb60             | 108             | 3                            | DPL23                      | 14                             | 13%                              | 29                     |
| NIG-68            | 99              | 3                            | DPL23                      | 25                             | 26%                              | 32                     |
| KERN              | 107             | 3                            | DPL23                      | 26                             | 25%                              | 59                     |
| ANT               | 106             | 3                            | DPL23                      | 17                             | 16%                              | 19                     |
| LEE               | 110             | 3                            | DPL23                      | 18                             | 17%                              | 85                     |
| CLE               | 94              | 3                            | DPL23                      | 17                             | 17%                              | 19                     |
| VL8               | 98              | 8                            | DPL21                      | 0                              | 0%                               | 81                     |
| MOT               | 110             | 3                            | Humlv318                   | 23                             | 22%                              | 38                     |
| GAR               | 108             | 3                            | DPL23                      | 26                             | 25%                              | 33                     |
| 32.B9             | 98              | 8                            | DPL21                      | 5                              | 5%                               | 81                     |
| PUG               | 108             | 3                            | Humlv318                   | 24                             | 23%                              | 19                     |
| T1                | 115             | 8                            | HUMLV801                   | 52                             | 50%                              | 6                      |
| RF-TS7            | 96              | 7                            | DPL18                      | 4                              | 4%                               | 60                     |
| YM-1              | 116             | 8                            | HUMLV801                   | 51                             | 49%                              | 75                     |
| K6H6              | 112             | 8                            | HUMLV801                   | 20                             | 19%                              | 44                     |
| K5C7              | 112             | 8                            | HUMLV801                   | 20                             | 19%                              | 44                     |
| K5B8              | 112             | 8                            | HUMLV801                   | 20                             | 19%                              | 44                     |
| K5G5              | 112             | 8                            | HUMLV801                   | 20                             | 19%                              | 44                     |
| K4B8              | 112             | 8                            | HUMLV801                   | 19                             | 18%                              | 44                     |
| K6F5              | 112             | 8                            | HUMLV801                   | 17                             | 16%                              | 44                     |
| HIL               | 108             | 3                            | DPL23                      | 22                             | 21%                              | 47                     |
| KIR               | 109             | 3                            | DPL23                      | 20                             | 19%                              | 19                     |
| CAP               | 109             | 3                            | DPL23                      | 19                             | 18%                              | 84                     |
| 1B8               | 110             | 3                            | DPL23                      | 22                             | 21%                              | 43                     |
| SHO               | 108             | 3                            | DPL23                      | 19                             | 18%                              | 19                     |
| HAN               | 108             | 3                            | DPL23                      | 20                             | 19%                              | 19                     |
| cML23             | 96              | 3                            | DPL23                      | 3                              | 3%                               | 12                     |
| PR-SJ1            | 96              | 3                            | DPL23                      | 7                              | 7%                               | 55                     |
| BAU               | 107             | 3                            | DPL23                      | 9                              | 9%                               | 5                      |
| TEX               | 99              | 3                            | DPL23                      | 8                              | 8%                               | 19                     |
| X(PET)            | 107             | 3                            | DPL23                      | 9                              | 9%                               | 51                     |
| DOY               | 106             | 3                            | DPL23                      | 9                              | 9%                               | 19                     |
| COT               | 106             | 3                            | DPL23                      | 13                             | 12%                              | 19                     |
| Pag-1             | 111             | 3                            | Humlv318                   | 5                              | 5%                               | 31                     |

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Table 2B: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed<br>family <sup>3</sup> | Germline<br>gene <sup>4</sup> | Diff. to<br>germline <sup>5</sup> | % diff. to<br>germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|---------------------------------|-------------------------------|-----------------------------------|-------------------------------------|------------------------|
| DIS               | 107             | 3                               | HuMlv318                      | 2                                 | 2%                                  | 19                     |
| WIT               | 108             | 3                               | HuMlv318                      | 7                                 | 7%                                  | 19                     |
| LRH               | 108             | 3                               | HuMlv318                      | 12                                | 11%                                 | 19                     |
| S1-1              | 108             | 3                               | HuMlv318                      | 12                                | 11%                                 | 52                     |
| DEL               | 108             | 3                               | HuMlv318                      | 14                                | 13%                                 | 17                     |
| TYR               | 108             | 3                               | HuMlv318                      | 11                                | 10%                                 | 19                     |
| J.RH              | 109             | 3                               | HuMlv318                      | 13                                | 12%                                 | 19                     |
| THO               | 112             | 2                               | DPL13                         | 38                                | 36%                                 | 26                     |
| LBV               | 113             | 1                               | DPL3                          | 38                                | 36%                                 | 2                      |
| WLT               | 112             | 1                               | DPL3                          | 33                                | 31%                                 | 14                     |
| SUT               | 112             | 2                               | DPL12                         | 37                                | 35%                                 | 65                     |

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Table 2C: rearranged human heavy chain sequences

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| 21/28             | 119             | 1                            | VH1-13-12                  | 0                              | 0,0%                             | 31                     |
| 8E10              | 123             | 1                            | VH1-13-12                  | 0                              | 0,0%                             | 31                     |
| MUC1-1            | 118             | 1                            | VH1-13-6                   | 4                              | 4,1%                             | 42                     |
| gF1               | 98              | 1                            | VH1-13-12                  | 10                             | 10,2%                            | 75                     |
| VHGL 1.2          | 98              | 1                            | VH1-13-6                   | 2                              | 2,0%                             | 26                     |
| HVIL1             | 98              | 1                            | VH1-13-6                   | 0                              | 0,0%                             | 81                     |
| RF-TS7            | 104             | 1                            | VH1-13-6                   | 3                              | 3,1%                             | 96                     |
| E55 1.A15         | 106             | 1                            | VH1-13-15                  | 1                              | 1,0%                             | 26                     |
| HA1L1             | 126             | 1                            | VH1-13-6                   | 7                              | 7,1%                             | 81                     |
| UC                | 123             | 1                            | VH1-13-6                   | 5                              | 5,1%                             | 115                    |
| WIL2              | 123             | 1                            | VH1-13-6                   | 6                              | 6,1%                             | 55                     |
| R3.5H5G           | 122             | 1                            | VH1-13-6                   | 10                             | 10,2%                            | 70                     |
| N89P2             | 123             | 1                            | VH1-13-16                  | 11                             | 11,2%                            | 77                     |
| mAb113            | 126             | 1                            | VH1-13-6                   | 10                             | 10,2%                            | 71                     |
| LS2S3-3           | 125             | 1                            | VH1-12-7                   | 5                              | 5,1%                             | 98                     |
| LS2S3-12a         | 125             | 1                            | VH1-12-7                   | 5                              | 5,1%                             | 98                     |
| LS2S3-5           | 125             | 1                            | VH1-12-7                   | 5                              | 5,1%                             | 98                     |
| LS2S3-12e         | 125             | 1                            | VH1-12-7                   | 5                              | 5,1%                             | 98                     |
| LS2S3-4           | 125             | 1                            | VH1-12-7                   | 5                              | 5,1%                             | 98                     |
| LS2S3-10          | 125             | 1                            | VH1-12-7                   | 5                              | 5,1%                             | 98                     |
| LS2S3-12d         | 125             | 1                            | VH1-12-7                   | 6                              | 6,1%                             | 98                     |
| LS2S3-8           | 125             | 1                            | VH1-12-7                   | 5                              | 5,1%                             | 98                     |
| LS2               | 125             | 1                            | VH1-12-7                   | 6                              | 6,1%                             | 113                    |
| LS4               | 105             | 1                            | VH1-12-7                   | 6                              | 6,1%                             | 113                    |
| LS5               | 125             | 1                            | VH1-12-7                   | 6                              | 6,1%                             | 113                    |
| LS1               | 125             | 1                            | VH1-12-7                   | 6                              | 6,1%                             | 113                    |
| LS6               | 125             | 1                            | VH1-12-7                   | 6                              | 6,1%                             | 113                    |
| LS8               | 125             | 1                            | VH1-12-7                   | 7                              | 7,1%                             | 113                    |
| THY-29            | 122             | 1                            | VH1-12-7                   | 0                              | 0,0%                             | 42                     |
| 1B9/F2            | 122             | 1                            | VH1-12-7                   | 10                             | 10,2%                            | 21                     |
| 51P1              | 122             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 105                    |
| NEI               | 127             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 55                     |
| AND               | 127             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 55                     |
| L7                | 127             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L22               | 124             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L24               | 127             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |

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Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| L26               | 116             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L33               | 119             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L34               | 117             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L36               | 118             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L39               | 120             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L41               | 120             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L42               | 125             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| VHGL 1.8          | 101             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 26                     |
| 783c              | 127             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 22                     |
| X17115            | 127             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 37                     |
| L25               | 124             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 54                     |
| L17               | 120             | 1                            | VH1-12-1                   | 1                              | 1,0%                             | 54                     |
| L30               | 127             | 1                            | VH1-12-1                   | 1                              | 1,0%                             | 54                     |
| L37               | 120             | 1                            | VH1-12-1                   | 1                              | 1,0%                             | 54                     |
| TNF-E7            | 116             | 1                            | VH1-12-1                   | 2                              | 2,0%                             | 42                     |
| mAb111            | 122             | 1                            | VH1-12-1                   | 7                              | 7,1%                             | 71                     |
| III-2R            | 122             | 1                            | VH1-12-9                   | 3                              | 3,1%                             | 70                     |
| KAS               | 121             | 1                            | VH1-12-1                   | 7                              | 7,1%                             | 79                     |
| YES8c             | 122             | 1                            | VH1-12-1                   | 8                              | 8,2%                             | 34                     |
| RF-TS1            | 123             | 1                            | VH1-12-1                   | 8                              | 8,2%                             | 82                     |
| BOR'              | 121             | 1                            | VH1-12-8                   | 7                              | 7,1%                             | 79                     |
| VHGL 1.9          | 101             | 1                            | VH1-12-1                   | 8                              | 8,2%                             | 26                     |
| mAb410.30F305     | 117             | 1                            | VH1-12-9                   | 5                              | 5,1%                             | 52                     |
| EV1-15            | 127             | 1                            | VH1-12-8                   | 10                             | 10,2%                            | 78                     |
| mAb112            | 122             | 1                            | VH1-12-1                   | 11                             | 11,2%                            | 71                     |
| EU                | 117             | 1                            | VH1-12-1                   | 11                             | 11,2%                            | 28                     |
| H210              | 127             | 1                            | VH1-12-1                   | 12                             | 12,2%                            | 66                     |
| TRANSGENE         | 104             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 111                    |
| CLL2-1            | 93              | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 30                     |
| CLL10 13-3        | 97              | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 29                     |
| LS7               | 99              | 1                            | VH1-12-7                   | 4                              | 4,1%                             | 113                    |
| ALL7-1            | 87              | 1                            | VH1-12-7                   | 0                              | 0,0%                             | 30                     |
| CLL3-1            | 91              | 1                            | VH1-12-7                   | 1                              | 1,0%                             | 30                     |
| ALL56-1           | 85              | 1                            | VH1-13-8                   | 0                              | 0,0%                             | 30                     |
| ALL1-1            | 87              | 1                            | VH1-13-6                   | 1                              | 1,0%                             | 30                     |
| ALL4-1            | 94              | 1                            | VH1-13-8                   | 0                              | 0,0%                             | 30                     |

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Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| ALL56 15-4        | 85              | 1                            | VH1-13-8                   | 5                              | 5,1%                             | 29                     |
| CLL4-1            | 88              | 1                            | VH1-13-1                   | 1                              | 1,0%                             | 30                     |
| Au92.1            | 98              | 1                            | VH1-12-5                   | 0                              | 0,0%                             | 49                     |
| RF-TS3            | 120             | 1                            | VH1-12-5                   | 1                              | 1,0%                             | 82                     |
| Au4.1             | 98              | 1                            | VH1-12-5                   | 1                              | 1,0%                             | 49                     |
| HP1               | 121             | 1                            | VH1-13-6                   | 13                             | 13,3%                            | 110                    |
| BLI               | 127             | 1                            | VH1-13-15                  | 5                              | 5,1%                             | 72                     |
| No.13             | 127             | 1                            | VH1-12-2                   | 19                             | 19,4%                            | 76                     |
| TR1.23            | 122             | 1                            | VH1-13-2                   | 23                             | 23,5%                            | 88                     |
| S1-1              | 125             | 1                            | VH1-12-2                   | 18                             | 18,4%                            | 76                     |
| TR1.10            | 119             | 1                            | VH1-13-12                  | 14                             | 14,3%                            | 88                     |
| E55 1.A2          | 102             | 1                            | VH1-13-15                  | 3                              | 3,1%                             | 26                     |
| SP2               | 119             | 1                            | VH1-13-6                   | 15                             | 15,3%                            | 89                     |
| TNF-H9G1          | 111             | 1                            | VH1-13-18                  | 2                              | 2,0%                             | 42                     |
| G3D10H            | 127             | 1                            | VH1-13-16                  | 19                             | 19,4%                            | 127                    |
| TR1.9             | 118             | 1                            | VH1-13-12                  | 14                             | 14,3%                            | 88                     |
| TR1.8             | 121             | 1                            | VH1-12-1                   | 24                             | 24,5%                            | 88                     |
| LUNm01            | 127             | 1                            | VH1-13-6                   | 22                             | 22,4%                            | 9                      |
| K1B12H            | 127             | 1                            | VH1-12-7                   | 23                             | 23,5%                            | 127                    |
| L3B2              | 99              | 1                            | VH1-13-6                   | 2                              | 2,0%                             | 46                     |
| ss2               | 100             | 1                            | VH1-13-6                   | 2                              | 2,0%                             | 46                     |
| No.86             | 124             | 1                            | VH1-12-1                   | 20                             | 20,4%                            | 76                     |
| TR1.6             | 124             | 1                            | VH1-12-1                   | 19                             | 19,4%                            | 88                     |
| ss7               | 99              | 1                            | VH1-12-7                   | 3                              | 3,1%                             | 46                     |
| s5B7              | 102             | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 46                     |
| s6A3              | 97              | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 46                     |
| ss6               | 99              | 1                            | VH1-12-1                   | 0                              | 0,0%                             | 46                     |
| L2H7              | 103             | 1                            | VH1-13-12                  | 0                              | 0,0%                             | 46                     |
| s6BG8             | 93              | 1                            | VH1-13-12                  | 0                              | 0,0%                             | 46                     |
| s6C9              | 107             | 1                            | VH1-13-12                  | 0                              | 0,0%                             | 46                     |
| HIV-b4            | 124             | 1                            | VH1-13-12                  | 21                             | 21,4%                            | 12                     |
| HIV-b12           | 124             | 1                            | VH1-13-12                  | 21                             | 21,4%                            | 12                     |
| L3G5              | 98              | 1                            | VH1-13-6                   | 1                              | 1,0%                             | 46                     |
| 22                | 115             | 1                            | VH1-13-6                   | 11                             | 11,2%                            | 118                    |
| L2A12             | 99              | 1                            | VH1-13-15                  | 3                              | 3,1%                             | 46                     |
| PHOX15            | 124             | 1                            | VH1-12-7                   | 20                             | 20,4%                            | 73                     |

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Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| LUNm03            | 127             | 1                            | VH1-1X-1                   | 18                             | 18,4%                            | 9                      |
| CEA4-8A           | 129             | 1                            | VH1-12-7                   | 1                              | 1,0%                             | 42                     |
| M60               | 121             | 2                            | VH2-31-3                   | 3                              | 3,0%                             | 103                    |
| HiH10             | 127             | 2                            | VH2-31-5                   | 9                              | 9,0%                             | 4                      |
| COR               | 119             | 2                            | VH2-31-2                   | 11                             | 11,0%                            | 91                     |
| 2-115-19          | 124             | 2                            | VH2-31-11                  | 8                              | 8,1%                             | 124                    |
| OU                | 125             | 2                            | VH2-31-14                  | 20                             | 25,6%                            | 92                     |
| HE                | 120             | 2                            | VH2-31-13                  | 19                             | 19,0%                            | 27                     |
| CLL33 40-1        | 78              | 2                            | VH2-31-5                   | 2                              | 2,0%                             | 29                     |
| E55 3.9           | 88              | 3                            | VH3-11-5                   | 7                              | 7,2%                             | 26                     |
| MTFC3             | 125             | 3                            | VH3-14-4                   | 21                             | 21,0%                            | 131                    |
| MTFC11            | 125             | 3                            | VH3-14-4                   | 21                             | 21,0%                            | 131                    |
| MTFJ1             | 114             | 3                            | VH3-14-4                   | 21                             | 21,0%                            | 131                    |
| MTFJ2             | 114             | 3                            | VH3-14-4                   | 21                             | 21,0%                            | 131                    |
| MTFUJ4            | 100             | 3                            | VH3-14-4                   | 21                             | 21,0%                            | 131                    |
| MTFUJ5            | 100             | 3                            | VH3-14-4                   | 21                             | 21,0%                            | 131                    |
| MTFUJ2            | 100             | 3                            | VH3-14-4                   | 22                             | 22,0%                            | 131                    |
| MTFC8             | 125             | 3                            | VH3-14-4                   | 23                             | 23,0%                            | 131                    |
| TD e Vq           | 113             | 3                            | VH3-14-4                   | 0                              | 0,0%                             | 16                     |
| rMTF              | 114             | 3                            | VH3-14-4                   | 5                              | 5,0%                             | 131                    |
| MTFUJ6            | 100             | 3                            | VH3-14-4                   | 10                             | 10,0%                            | 131                    |
| RF-KES            | 107             | 3                            | VH3-14-4                   | 9                              | 9,0%                             | 85                     |
| N51P8             | 126             | 3                            | VH3-14-1                   | 9                              | 9,0%                             | 77                     |
| TEI               | 119             | 3                            | VH3-13-8                   | 21                             | 21,4%                            | 20                     |
| 33.H11            | 115             | 3                            | VH3-13-19                  | 10                             | 10,2%                            | 129                    |
| SB1/D8            | 101             | 3                            | VH3-1X-8                   | 14                             | 14,0%                            | 2                      |
| 38P1              | 119             | 3                            | VH3-11-3                   | 0                              | 0,0%                             | 104                    |
| BRO'IGM           | 119             | 3                            | VH3-11-3                   | 13                             | 13,4%                            | 19                     |
| NIE               | 119             | 3                            | VH3-13-7                   | 15                             | 15,3%                            | 87                     |
| 3D6               | 126             | 3                            | VH3-13-26                  | 5                              | 5,1%                             | 35                     |
| ZM1-1             | 112             | 3                            | VH3-11-3                   | 8                              | 8,2%                             | 5                      |
| E55 3.15          | 110             | 3                            | VH3-13-26                  | 0                              | 0,0%                             | 26                     |
| gF9               | 108             | 3                            | VH3-13-8                   | 15                             | 15,3%                            | 75                     |
| THY-32            | 120             | 3                            | VH3-13-26                  | 3                              | 3,1%                             | 42                     |
| RF-KL5            | 100             | 3                            | VH3-13-26                  | 5                              | 5,1%                             | 96                     |
| OST577            | 122             | 3                            | VH3-13-13                  | 6                              | 6,1%                             | 5                      |

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Table 2C: (continued)

| Name <sup>1</sup>   | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|---------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| BO                  | 113             | 3                            | VH3-13-19                  | 15                             | 15,3%                            | 10                     |
| TT125               | 121             | 3                            | VH3-13-10                  | 15                             | 15,3%                            | 64                     |
| 2-115-58            | 127             | 3                            | VH3-13-10                  | 11                             | 11,2%                            | 124                    |
| KOL                 | 126             | 3                            | VH3-13-14                  | 16                             | 16,3%                            | 102                    |
| mAb60               | 118             | 3                            | VH3-13-17                  | 14                             | 14,3%                            | 45                     |
| RF-AN               | 106             | 3                            | VH3-13-26                  | 8                              | 8,2%                             | 85                     |
| BUT                 | 115             | 3                            | VH3-11-6                   | 13                             | 13,4%                            | 119                    |
| KOL-based CAMPATH-9 | 118             | 3                            | VH3-13-13                  | 16                             | 16,3%                            | 41                     |
| B1                  | 119             | 3                            | VH3-13-19                  | 13                             | 13,3%                            | 53                     |
| N98P1               | 127             | 3                            | VH3-13-1                   | 13                             | 13,3%                            | 77                     |
| TT117               | 107             | 3                            | VH3-13-10                  | 12                             | 12,2%                            | 64                     |
| WEA                 | 114             | 3                            | VH3-13-12                  | 15                             | 15,3%                            | 40                     |
| HIL                 | 120             | 3                            | VH3-13-14                  | 14                             | 14,3%                            | 23                     |
| s5A10               | 97              | 3                            | VH3-13-14                  | 0                              | 0,0%                             | 46                     |
| s5D11               | 98              | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 46                     |
| s6C8                | 100             | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 46                     |
| s6H12               | 98              | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 46                     |
| VH10.7              | 119             | 3                            | VH3-13-14                  | 16                             | 16,3%                            | 128                    |
| HIV-loop2           | 126             | 3                            | VH3-13-7                   | 16                             | 16,3%                            | 12                     |
| HIV-loop35          | 126             | 3                            | VH3-13-7                   | 16                             | 16,3%                            | 12                     |
| TRO                 | 122             | 3                            | VH3-13-1                   | 13                             | 13,3%                            | 61                     |
| SA-4B               | 123             | 3                            | VH3-13-1                   | 15                             | 15,3%                            | 125                    |
| L2B5                | 98              | 3                            | VH3-13-13                  | 0                              | 0,0%                             | 46                     |
| s6E11               | 95              | 3                            | VH3-13-13                  | 0                              | 0,0%                             | 46                     |
| s6H7                | 100             | 3                            | VH3-13-13                  | 0                              | 0,0%                             | 46                     |
| ss1                 | 102             | 3                            | VH3-13-13                  | 0                              | 0,0%                             | 46                     |
| ss8                 | 94              | 3                            | VH3-13-13                  | 0                              | 0,0%                             | 46                     |
| DOB                 | 120             | 3                            | VH3-13-26                  | 21                             | 21,4%                            | 116                    |
| THY-33              | 115             | 3                            | VH3-13-15                  | 20                             | 20,4%                            | 42                     |
| NOV                 | 118             | 3                            | VH3-13-19                  | 14                             | 14,3%                            | 38                     |
| rsv13H              | 120             | 3                            | VH3-13-24                  | 20                             | 20,4%                            | 11                     |
| L3G11               | 98              | 3                            | VH3-13-20                  | 2                              | 2,0%                             | 46                     |
| L2E8                | 99              | 3                            | VH3-13-19                  | 0                              | 0,0%                             | 46                     |
| L2D10               | 101             | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 46                     |
| L2E7                | 98              | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 46                     |

Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| L3A10             | 100             | 3                            | VH3-13-24                  | 0                              | 0,0%                             | 46                     |
| L2E5              | 97              | 3                            | VH3-13-2                   | 1                              | 1,0%                             | 46                     |
| BUR               | 119             | 3                            | VH3-13-7                   | 21                             | 21,4%                            | 67                     |
| s4D5              | 107             | 3                            | VH3-11-3                   | 1                              | 1,0%                             | 46                     |
| 19                | 116             | 3                            | VH3-13-16                  | 4                              | 4,1%                             | 118                    |
| s5D4              | 99              | 3                            | VH3-13-1                   | 0                              | 0,0%                             | 46                     |
| s6A8              | 100             | 3                            | VH3-13-1                   | 0                              | 0,0%                             | 46                     |
| HIV-loop13        | 123             | 3                            | VH3-13-12                  | 17                             | 17,3%                            | 12                     |
| TR1.32            | 112             | 3                            | VH3-11-8                   | 18                             | 18,6%                            | 88                     |
| L2B10             | 97              | 3                            | VH3-11-3                   | 1                              | 1,0%                             | 46                     |
| TR1.5             | 114             | 3                            | VH3-11-8                   | 21                             | 21,6%                            | 88                     |
| s6H9              | 101             | 3                            | VH3-13-25                  | 0                              | 0,0%                             | 46                     |
| 8                 | 112             | 3                            | VH3-13-1                   | 6                              | 6,1%                             | 118                    |
| 23                | 115             | 3                            | VH3-13-1                   | 6                              | 6,1%                             | 118                    |
| 7                 | 115             | 3                            | VH3-13-1                   | 4                              | 4,1%                             | 118                    |
| TR1.3             | 120             | 3                            | VH3-11-8                   | 20                             | 20,6%                            | 88                     |
| 18/2              | 125             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 32                     |
| 18/9              | 125             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 31                     |
| 30P1              | 119             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 106                    |
| HF2-1/17          | 125             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 8                      |
| A77               | 109             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 44                     |
| B19.7             | 108             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 44                     |
| M43               | 119             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 103                    |
| 1/17              | 125             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 31                     |
| 18/17             | 125             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 31                     |
| E54 3.4           | 109             | 3                            | VH3-13-10                  | 0                              | 0,0%                             | 26                     |
| LAMBDA-VH26       | 98              | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 95                     |
| E54 3.8           | 111             | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 26                     |
| GL16              | 106             | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 44                     |
| 4G12              | 125             | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 56                     |
| A73               | 106             | 3                            | VH3-13-10                  | 2                              | 2,0%                             | 44                     |
| AL1.3             | 111             | 3                            | VH3-13-10                  | 3                              | 3,1%                             | 117                    |
| 3.A290            | 118             | 3                            | VH3-13-10                  | 2                              | 2,0%                             | 108                    |
| Ab18              | 127             | 3                            | VH3-13-8                   | 2                              | 2,0%                             | 100                    |
| E54 3.3           | 105             | 3                            | VH3-13-10                  | 3                              | 3,1%                             | 26                     |
| 35G6              | 121             | 3                            | VH3-13-10                  | 3                              | 3,1%                             | 57                     |



Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| A95               | 107             | 3                            | VH3-13-10                  | 5                              | 5,1%                             | 44                     |
| Ab25              | 128             | 3                            | VH3-13-10                  | 5                              | 5,1%                             | 100                    |
| N87               | 126             | 3                            | VH3-13-10                  | 4                              | 4,1%                             | 77                     |
| ED8.4             | 99              | 3                            | VH3-13-10                  | 6                              | 6,1%                             | 2                      |
| RF-KL1            | 122             | 3                            | VH3-13-10                  | 6                              | 6,1%                             | 82                     |
| AL1.1             | 112             | 3                            | VH3-13-10                  | 2                              | 2,0%                             | 117                    |
| AL3.11            | 102             | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 117                    |
| 32.B9             | 127             | 3                            | VH3-13-8                   | 6                              | 6,1%                             | 129—                   |
| TK1               | 109             | 3                            | VH3-13-10                  | 2                              | 2,0%                             | 117                    |
| POP               | 123             | 3                            | VH3-13-10                  | 8                              | 8,2%                             | 115                    |
| 9F2H              | 127             | 3                            | VH3-13-10                  | 9                              | 9,2%                             | 127                    |
| VD                | 115             | 3                            | VH3-13-10                  | 9                              | 9,2%                             | 10                     |
| Vh38Cl.10         | 121             | 3                            | VH3-13-10                  | 8                              | 8,2%                             | 74                     |
| Vh38Cl.9          | 121             | 3                            | VH3-13-10                  | 8                              | 8,2%                             | 74                     |
| Vh38Cl.8          | 121             | 3                            | VH3-13-10                  | 8                              | 8,2%                             | 74                     |
| 63P1              | 120             | 3                            | VH3-11-8                   | 0                              | 0,0%                             | 104                    |
| 60P2              | 117             | 3                            | VH3-11-8                   | 0                              | 0,0%                             | 104                    |
| AL3.5             | 90              | 3                            | VH3-13-10                  | 2                              | 2,0%                             | 117                    |
| GF4/I.1           | 123             | 3                            | VH3-13-10                  | 10                             | 10,2%                            | 39                     |
| Ab21              | 126             | 3                            | VH3-13-10                  | 12                             | 12,2%                            | 100                    |
| TD d Vp           | 118             | 3                            | VH3-13-17                  | 2                              | 2,0%                             | 16                     |
| Vh38Cl.4          | 119             | 3                            | VH3-13-10                  | 8                              | 8,2%                             | 74                     |
| Vh38Cl.5          | 119             | 3                            | VH3-13-10                  | 8                              | 8,2%                             | 74                     |
| AL3.4             | 104             | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 117                    |
| FOG1-A3           | 115             | 3                            | VH3-13-19                  | 2                              | 2,0%                             | 42                     |
| HA3D1             | 117             | 3                            | VH3-13-21                  | 1                              | 1,0%                             | 81                     |
| E54 3.2           | 112             | 3                            | VH3-13-24                  | 0                              | 0,0%                             | 26                     |
| mAb52             | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| mAb53             | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| mAb56             | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| mAb57             | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| mAb58             | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| mAb59             | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| mAb105            | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| mAb107            | 128             | 3                            | VH3-13-12                  | 2                              | 2,0%                             | 51                     |
| E55 3.14          | 110             | 3                            | VH3-13-19                  | 0                              | 0,0%                             | 26                     |

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Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| F13-28            | 106             | 3                            | VH3-13-19                  | 1                              | 1,0%                             | 94                     |
| mAb55             | 127             | 3                            | VH3-13-18                  | 4                              | 4,1%                             | 51                     |
| YSE               | 117             | 3                            | VH3-13-24                  | 6                              | 6,1%                             | 72                     |
| E55 3.23          | 106             | 3                            | VH3-13-19                  | 2                              | 2,0%                             | 26                     |
| RF-TS5            | 101             | 3                            | VH3-13-1                   | 3                              | 3,1%                             | 85                     |
| N42P5             | 124             | 3                            | VH3-13-2                   | 7                              | 7,1%                             | 77                     |
| FOG1-H6           | 110             | 3                            | VH3-13-16                  | 7                              | 7,1%                             | 42                     |
| O-81              | 115             | 3                            | VH3-13-19                  | 11                             | 11,2%                            | 47                     |
| HIV-s8            | 122             | 3                            | VH3-13-12                  | 11                             | 11,2%                            | 12                     |
| mAb114            | 125             | 3                            | VH3-13-19                  | 12                             | 12,2%                            | 71                     |
| 33.F12            | 116             | 3                            | VH3-13-2                   | 4                              | 4,1%                             | 129                    |
| 4B4               | 119             | 3                            | VH3-1X-3                   | 0                              | 0,0%                             | 101                    |
| M26               | 123             | 3                            | VH3-1X-3                   | 0                              | 0,0%                             | 103                    |
| VHGL 3.1          | 100             | 3                            | VH3-1X-3                   | 0                              | 0,0%                             | 26                     |
| E55 3.13          | 113             | 3                            | VH3-1X-3                   | 1                              | 1,0%                             | 26                     |
| SB5/D6            | 101             | 3                            | VH3-1X-6                   | 3                              | 3,0%                             | 2                      |
| RAY4              | 101             | 3                            | VH3-1X-6                   | 3                              | 3,0%                             | 2                      |
| 82-D V-D          | 106             | 3                            | VH3-1X-3                   | 5                              | 5,0%                             | 112                    |
| MAL               | 129             | 3                            | VH3-1X-3                   | 5                              | 5,0%                             | 72                     |
| LOC               | 123             | 3                            | VH3-1X-6                   | 5                              | 5,0%                             | 72                     |
| LSF2              | 101             | 3                            | VH3-1X-6                   | 11                             | 11,0%                            | 2                      |
| HIB RC3           | 100             | 3                            | VH3-1X-6                   | 11                             | 11,0%                            | 1                      |
| 56P1              | 119             | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 104                    |
| M72               | 122             | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 103                    |
| M74               | 121             | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 103                    |
| E54 3.5           | 105             | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 26                     |
| 2E7               | 123             | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 63                     |
| 2P1               | 117             | 3                            | VH3-13-7                   | 0                              | 0,0%                             | 104                    |
| RF-SJ2            | 127             | 3                            | VH3-13-7                   | 1                              | 1,0%                             | 83                     |
| PR-TS1            | 114             | 3                            | VH3-13-7                   | 1                              | 1,0%                             | 85                     |
| KIM46H            | 127             | 3                            | VH3-13-13                  | 0                              | 0,0%                             | 18                     |
| E55 3.6           | 108             | 3                            | VH3-13-7                   | 2                              | 2,0%                             | 26                     |
| E55 3.10          | 107             | 3                            | VH3-13-13                  | 1                              | 1,0%                             | 26                     |
| 3.B6              | 114             | 3                            | VH3-13-13                  | 1                              | 1,0%                             | 108                    |
| E54 3.6           | 110             | 3                            | VH3-13-13                  | 1                              | 1,0%                             | 26                     |
| FL2-2             | 114             | 3                            | VH3-13-13                  | 1                              | 1,0%                             | 80                     |

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Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| RF-SJ3            | 112             | 3                            | VH3-13-7                   | 2                              | 2,0%                             | 85                     |
| E55 3.5           | 105             | 3                            | VH3-13-14                  | 1                              | 1,0%                             | 26                     |
| BSA3              | 121             | 3                            | VH3-13-13                  | 1                              | 1,0%                             | 73                     |
| HMST-1            | 119             | 3                            | VH3-13-7                   | 3                              | 3,1%                             | 130                    |
| RF-TS2            | 126             | 3                            | VH3-13-13                  | 4                              | 4,1%                             | 82                     |
| E55 3.12          | 109             | 3                            | VH3-13-15                  | 0                              | 0,0%                             | 26                     |
| 19.E7             | 126             | 3                            | VH3-13-14                  | 3                              | 3,1%                             | 129                    |
| 11-50             | 119             | 3                            | VH3-13-13                  | 6                              | 6,1%                             | 130                    |
| E29.1             | 120             | 3                            | VH3-13-15                  | 2                              | 2,0%                             | 25                     |
| E55 3.16          | 108             | 3                            | VH3-13-7                   | 6                              | 6,1%                             | 26                     |
| TNF-E1            | 117             | 3                            | VH3-13-7                   | 7                              | 7,1%                             | 42                     |
| RF-SJ1            | 127             | 3                            | VH3-13-13                  | 6                              | 6,1%                             | 83                     |
| FOG1-A4           | 116             | 3                            | VH3-13-7                   | 8                              | 8,2%                             | 42                     |
| TNF-A1            | 117             | 3                            | VH3-13-15                  | 4                              | 4,1%                             | 42                     |
| PR-SJ2            | 107             | 3                            | VH3-13-14                  | 8                              | 8,2%                             | 85                     |
| HN.14             | 124             | 3                            | VH3-13-13                  | 10                             | 10,2%                            | 33                     |
| CAM'              | 121             | 3                            | VH3-13-7                   | 12                             | 12,2%                            | 65                     |
| HIV-B8            | 125             | 3                            | VH3-13-7                   | 9                              | 9,2%                             | 12                     |
| HIV-b27           | 125             | 3                            | VH3-13-7                   | 9                              | 9,2%                             | 12                     |
| HIV-b8            | 125             | 3                            | VH3-13-7                   | 9                              | 9,2%                             | 12                     |
| HIV-s4            | 125             | 3                            | VH3-13-7                   | 9                              | 9,2%                             | 12                     |
| HIV-B26           | 125             | 3                            | VH3-13-7                   | 9                              | 9,2%                             | 12                     |
| HIV-B35           | 125             | 3                            | VH3-13-7                   | 10                             | 10,2%                            | 12                     |
| HIV-b18           | 125             | 3                            | VH3-13-7                   | 10                             | 10,2%                            | 12                     |
| HIV-b22           | 125             | 3                            | VH3-13-7                   | 11                             | 11,2%                            | 12                     |
| HIV-b13           | 125             | 3                            | VH3-13-7                   | 12                             | 12,2%                            | 12                     |
| 333               | 117             | 3                            | VH3-14-4                   | 24                             | 24,0%                            | 24                     |
| 1H1               | 120             | 3                            | VH3-14-4                   | 24                             | 24,0%                            | 24                     |
| 1B11              | 120             | 3                            | VH3-14-4                   | 23                             | 23,0%                            | 24                     |
| CLL30 2-3         | 86              | 3                            | VH3-13-19                  | 1                              | 1,0%                             | 29                     |
| GA                | 110             | 3                            | VH3-13-7                   | 19                             | 19,4%                            | 36                     |
| JeB               | 99              | 3                            | VH3-13-14                  | 3                              | 3,1%                             | 7                      |
| GAL               | 110             | 3                            | VH3-13-19                  | 10                             | 10,2%                            | 126                    |
| K6H6              | 119             | 3                            | VH3-1X-6                   | 18                             | 18,0%                            | 60                     |
| K4B8              | 119             | 3                            | VH3-1X-6                   | 18                             | 18,0%                            | 60                     |
| K5B8              | 119             | 3                            | VH3-1X-6                   | 18                             | 18,0%                            | 60                     |

Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| K5C7              | 119             | 3                            | VH3-1X-6                   | 19                             | 19,0%                            | 60                     |
| K5G5              | 119             | 3                            | VH3-1X-6                   | 19                             | 19,0%                            | 60                     |
| K6F5              | 119             | 3                            | VH3-1X-6                   | 19                             | 19,0%                            | 60                     |
| AL3.16            | 98              | 3                            | VH3-13-10                  | 1                              | 1,0%                             | 117                    |
| N86P2             | 98              | 3                            | VH3-13-10                  | 3                              | 3,1%                             | 77                     |
| N54P6             | 95              | 3                            | VH3-13-16                  | 7                              | 7,1%                             | 77                     |
| LAMBDA HT112-1    | 126             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 3                      |
| HY18              | 121             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 43                     |
| mAb63             | 126             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 45                     |
| FS-3              | 105             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 86                     |
| FS-5              | 111             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 86                     |
| FS-7              | 107             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 86                     |
| FS-8              | 110             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 86                     |
| PR-TS2            | 105             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 85                     |
| RF-TMC            | 102             | 4                            | VH4-11-2                   | 0                              | 0,0%                             | 85                     |
| mAb216            | 122             | 4                            | VH4-11-2                   | 1                              | 1,0%                             | 15                     |
| mAb410.7.F91      | 122             | 4                            | VH4-11-2                   | 1                              | 1,0%                             | 52                     |
| mAbA6H4C5         | 124             | 4                            | VH4-11-2                   | 1                              | 1,0%                             | 15                     |
| Ab44              | 127             | 4                            | VH4-11-2                   | 2                              | 2,1%                             | 100                    |
| 6H-3C4            | 124             | 4                            | VH4-11-2                   | 3                              | 3,1%                             | 59                     |
| FS-6              | 108             | 4                            | VH4-11-2                   | 6                              | 6,2%                             | 86                     |
| FS-2              | 114             | 4                            | VH4-11-2                   | 6                              | 6,2%                             | 84                     |
| HIG1              | 126             | 4                            | VH4-11-2                   | 7                              | 7,2%                             | 62                     |
| FS-4              | 105             | 4                            | VH4-11-2                   | 8                              | 8,2%                             | 86                     |
| SA-4A             | 123             | 4                            | VH4-11-2                   | 9                              | 9,3%                             | 125                    |
| LES-C             | 119             | 4                            | VH4-11-2                   | 10                             | 10,3%                            | 99                     |
| DI                | 78              | 4                            | VH4-11-9                   | 16                             | 16,5%                            | 58                     |
| Ab26              | 126             | 4                            | VH4-31-4                   | 8                              | 8,1%                             | 100                    |
| TS2               | 124             | 4                            | VH4-31-12                  | 15                             | 15,2%                            | 110                    |
| 265-695           | 115             | 4                            | VH4-11-7                   | 16                             | 16,5%                            | 5                      |
| WAH               | 129             | 4                            | VH4-31-13                  | 19                             | 19,2%                            | 93                     |
| 268-D             | 122             | 4                            | VH4-11-8                   | 22                             | 22,7%                            | 6                      |
| 58P2              | 118             | 4                            | VH4-11-8                   | 0                              | 0,0%                             | 104                    |
| mAb67             | 128             | 4                            | VH4-21-4                   | 1                              | 1,0%                             | 45                     |
| 4.L39             | 115             | 4                            | VH4-11-8                   | 2                              | 2,1%                             | 108                    |
| mF7               | 111             | 4                            | VH4-31-13                  | 3                              | 3,0%                             | 75                     |

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Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| 33.C9             | 122             | 4                            | VH4-21-5                   | 7                              | 7,1%                             | 129                    |
| Pag-1             | 124             | 4                            | VH4-11-16                  | 5                              | 5,2%                             | 50                     |
| B3                | 123             | 4                            | VH4-21-3                   | 8                              | 8,2%                             | 53                     |
| IC4               | 120             | 4                            | VH4-11-8                   | 6                              | 6,2%                             | 70                     |
| C6B2              | 127             | 4                            | VH4-31-12                  | 4                              | 4,0%                             | 48                     |
| N78               | 118             | 4                            | VH4-11-9                   | 11                             | 11,3%                            | 77                     |
| B2                | 109             | 4                            | VH4-11-8                   | 12                             | 12,4%                            | 53                     |
| WRD2              | 123             | 4                            | VH4-11-12                  | 6                              | 6,2%                             | 90                     |
| mAb426.4.2F20     | 126             | 4                            | VH4-11-8                   | 2                              | 2,1%                             | 52                     |
| E54 4.58          | 115             | 4                            | VH4-11-8                   | 1                              | 1,0%                             | 26                     |
| WRD6              | 123             | 4                            | VH4-11-12                  | 10                             | 10,3%                            | 90                     |
| mAb426.12.3F1.4   | 122             | 4                            | VH4-11-9                   | 4                              | 4,1%                             | 52                     |
| E54 4.2           | 108             | 4                            | VH4-21-6                   | 2                              | 2,0%                             | 26                     |
| WIL               | 127             | 4                            | VH4-31-13                  | 0                              | 0,0%                             | 90                     |
| COF               | 126             | 4                            | VH4-31-13                  | 0                              | 0,0%                             | 90                     |
| LAR               | 122             | 4                            | VH4-31-13                  | 2                              | 2,0%                             | 90                     |
| WAT               | 125             | 4                            | VH4-31-13                  | 4                              | 4,0%                             | 90                     |
| mAb61             | 123             | 4                            | VH4-31-13                  | 5                              | 5,1%                             | 45                     |
| WAG               | 127             | 4                            | VH4-31-4                   | 0                              | 0,0%                             | 90                     |
| RF-SJ4            | 108             | 4                            | VH4-31-12                  | 2                              | 2,0%                             | 85                     |
| E54 4.4           | 110             | 4                            | VH4-11-7                   | 0                              | 0,0%                             | 26                     |
| E55 4.A1          | 108             | 4                            | VH4-11-7                   | 0                              | 0,0%                             | 26                     |
| PR-SJ1            | 103             | 4                            | VH4-11-7                   | 1                              | 1,0%                             | 85                     |
| E54 4.23          | 111             | 4                            | VH4-11-7                   | 1                              | 1,0%                             | 26                     |
| CLL7 7-2          | 97              | 4                            | VH4-11-12                  | 0                              | 0,0%                             | 29                     |
| 37P1              | 95              | 4                            | VH4-11-12                  | 0                              | 0,0%                             | 104                    |
| ALL52 30-2        | 91              | 4                            | VH4-31-12                  | 4                              | 4,0%                             | 29                     |
| EBV-21            | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 13                     |
| CB-4              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 13                     |
| CLL-12            | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 13                     |
| L3-4              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 13                     |
| CLL11             | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CORD3             | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CORD4             | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CORD8             | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CORD9             | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |

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Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| CD+1              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CD+3              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CD+4              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CD-1              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CD-5              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| VERG14            | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| PBL1              | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| PBL10             | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| STRAb SA-1A       | 127             | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 125                    |
| DOB'              | 122             | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 97                     |
| VERG5             | 98              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| PBL2              | 98              | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 17                     |
| Tu16              | 119             | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 49                     |
| PBL12             | 98              | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 17                     |
| CD+2              | 98              | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 17                     |
| CORD10            | 98              | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 17                     |
| PBL9              | 98              | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 17                     |
| CORD2             | 98              | 5                            | VH5-12-1                   | 2                              | 2,0%                             | 17                     |
| PBL6              | 98              | 5                            | VH5-12-1                   | 2                              | 2,0%                             | 17                     |
| CORD5             | 98              | 5                            | VH5-12-1                   | 2                              | 2,0%                             | 17                     |
| CD-2              | 98              | 5                            | VH5-12-1                   | 2                              | 2,0%                             | 17                     |
| CORD1             | 98              | 5                            | VH5-12-1                   | 2                              | 2,0%                             | 17                     |
| CD-3              | 98              | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 17                     |
| VERG4             | 98              | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 17                     |
| PBL13             | 98              | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 17                     |
| PBL7              | 98              | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 17                     |
| HAN               | 119             | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 97                     |
| VERG3             | 98              | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 17                     |
| PBL3              | 98              | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 17                     |
| VERG7             | 98              | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 17                     |
| PBL5              | 94              | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 17                     |
| CD-4              | 98              | 5                            | VH5-12-1                   | 4                              | 4,1%                             | 17                     |
| CLL10             | 98              | 5                            | VH5-12-1                   | 4                              | 4,1%                             | 17                     |
| PBL11             | 98              | 5                            | VH5-12-1                   | 4                              | 4,1%                             | 17                     |
| CORD6             | 98              | 5                            | VH5-12-1                   | 4                              | 4,1%                             | 17                     |
| VERG2             | 98              | 5                            | VH5-12-1                   | 5                              | 5,1%                             | 17                     |

Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| 83P2              | 119             | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 103                    |
| VERG9             | 98              | 5                            | VH5-12-1                   | 6                              | 6,1%                             | 17                     |
| CLL6              | 98              | 5                            | VH5-12-1                   | 6                              | 6,1%                             | 17                     |
| PBL8              | 98              | 5                            | VH5-12-1                   | 7                              | 7,1%                             | 17                     |
| Ab2022            | 120             | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 100                    |
| CAV               | 127             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 97                     |
| HOW'              | 120             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 97                     |
| PET               | 127             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 97                     |
| ANG               | 121             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 97                     |
| KER               | 121             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 97                     |
| 5.M13             | 118             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 107                    |
| Au2.1             | 118             | 5                            | VH5-12-4                   | 1                              | 1,0%                             | 49                     |
| WS1               | 126             | 5                            | VH5-12-1                   | 9                              | 9,2%                             | 110                    |
| TD Vn             | 98              | 5                            | VH5-12-4                   | 1                              | 1,0%                             | 16                     |
| TEL13             | 116             | 5                            | VH5-12-1                   | 9                              | 9,2%                             | 73                     |
| E55 5.237         | 112             | 5                            | VH5-12-4                   | 2                              | 2,0%                             | 26                     |
| VERG1             | 98              | 5                            | VH5-12-1                   | 10                             | 10,2%                            | 17                     |
| CD4-74            | 117             | 5                            | VH5-12-1                   | 10                             | 10,2%                            | 42                     |
| 257-D             | 125             | 5                            | VH5-12-1                   | 11                             | 11,2%                            | 6                      |
| CLL4              | 98              | 5                            | VH5-12-1                   | 11                             | 11,2%                            | 17                     |
| CLL8              | 98              | 5                            | VH5-12-1                   | 11                             | 11,2%                            | 17                     |
| Ab2               | 124             | 5                            | VH5-12-1                   | 12                             | 12,2%                            | 120                    |
| Vh383ex           | 98              | 5                            | VH5-12-1                   | 12                             | 12,2%                            | 120                    |
| CLL3              | 98              | 5                            | VH5-12-2                   | 11                             | 11,2%                            | 17                     |
| Au59.1            | 122             | 5                            | VH5-12-1                   | 12                             | 12,2%                            | 49                     |
| TEL16             | 117             | 5                            | VH5-12-1                   | 12                             | 12,2%                            | 73                     |
| M61               | 104             | 5                            | VH5-12-1                   | 0                              | 0,0%                             | 103                    |
| Tu0               | 99              | 5                            | VH5-12-1                   | 5                              | 5,1%                             | 49                     |
| P2-51             | 122             | 5                            | VH5-12-1                   | 13                             | 13,3%                            | 121                    |
| P2-54             | 122             | 5                            | VH5-12-1                   | 11                             | 11,2%                            | 121                    |
| P1-56             | 119             | 5                            | VH5-12-1                   | 9                              | 9,2%                             | 121                    |
| P2-53             | 122             | 5                            | VH5-12-1                   | 10                             | 10,2%                            | 121                    |
| P1-51             | 123             | 5                            | VH5-12-1                   | 19                             | 19,4%                            | 121                    |
| P1-54             | 123             | 5                            | VH5-12-1                   | 3                              | 3,1%                             | 121                    |
| P3-69             | 127             | 5                            | VH5-12-1                   | 4                              | 4,1%                             | 121                    |
| P3-9              | 119             | 5                            | VH5-12-1                   | 4                              | 4,1%                             | 121                    |

Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| 1-185-37          | 125             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 124                    |
| 1-187-29          | 125             | 5                            | VH5-12-4                   | 0                              | 0,0%                             | 124                    |
| P1-58             | 128             | 5                            | VH5-12-4                   | 10                             | 10,2%                            | 121                    |
| P2-57             | 118             | 5                            | VH5-12-4                   | 3                              | 3,1%                             | 121                    |
| P2-55             | 123             | 5                            | VH5-12-1                   | 5                              | 5,1%                             | 121                    |
| P2-56             | 123             | 5                            | VH5-12-1                   | 20                             | 20,4%                            | 121                    |
| P2-52             | 122             | 5                            | VH5-12-1                   | 11                             | 11,2%                            | 121                    |
| P3-60             | 122             | 5                            | VH5-12-1                   | 8                              | 8,2%                             | 121                    |
| P1-57             | 123             | 5                            | VH5-12-1                   | 4                              | 4,1%                             | 121                    |
| P1-55             | 122             | 5                            | VH5-12-1                   | 14                             | 14,3%                            | 121                    |
| MD3-4             | 128             | 5                            | VH5-12-4                   | 12                             | 12,2%                            | 5                      |
| P1-52             | 121             | 5                            | VH5-12-1                   | 11                             | 11,2%                            | 121                    |
| CLL5              | 98              | 5                            | VH5-12-1                   | 13                             | 13,3%                            | 17                     |
| CLL7              | 98              | 5                            | VH5-12-1                   | 14                             | 14,3%                            | 17                     |
| L2F10             | 100             | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 46                     |
| L3B6              | 98              | 5                            | VH5-12-1                   | 1                              | 1,0%                             | 46                     |
| VH6.A12           | 119             | 6                            | VH6-35-1                   | 13                             | 12,9%                            | 122                    |
| s5A9              | 102             | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 46                     |
| s6G4              | 99              | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 46                     |
| ss3               | 99              | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 46                     |
| 6-1G1             | 101             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 14                     |
| F19L16            | 107             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 68                     |
| L16               | 120             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 69                     |
| M71               | 121             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 103                    |
| ML1               | 120             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 69                     |
| F19ML1            | 107             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 68                     |
| 15P1              | 127             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 104                    |
| VH6.N1            | 121             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N11           | 123             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N12           | 123             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N2            | 125             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N5            | 125             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N6            | 127             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N7            | 126             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N8            | 123             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.N9            | 123             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |



Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| VH6.N10           | 123             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.A3            | 123             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.A1            | 124             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| VH6.A4            | 120             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| E55 6.16          | 116             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 26                     |
| E55 6.17          | 120             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 26                     |
| E55 6.6           | 120             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 26                     |
| VHGL 6.3          | 102             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 26                     |
| CB-201            | 118             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 109                    |
| VH6.N4            | 122             | 6                            | VH6-35-1                   | 0                              | 0,0%                             | 122                    |
| E54 6.4           | 109             | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 26                     |
| VH6.A6            | 126             | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 122                    |
| E55 6.14          | 120             | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 26                     |
| E54 6.6           | 107             | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 26                     |
| E55 6.10          | 112             | 6                            | VH6-35-1                   | 1                              | 1,0%                             | 26                     |
| E54 6.1           | 107             | 6                            | VH6-35-1                   | 2                              | 2,0%                             | 26                     |
| E55 6.13          | 120             | 6                            | VH6-35-1                   | 2                              | 2,0%                             | 26                     |
| E55 6.3           | 120             | 6                            | VH6-35-1                   | 2                              | 2,0%                             | 26                     |
| E55 6.7           | 116             | 6                            | VH6-35-1                   | 2                              | 2,0%                             | 26                     |
| E55 6.2           | 120             | 6                            | VH6-35-1                   | 2                              | 2,0%                             | 26                     |
| E55 6.X           | 111             | 6                            | VH6-35-1                   | 2                              | 2,0%                             | 26                     |
| E55 6.11          | 111             | 6                            | VH6-35-1                   | 3                              | 3,0%                             | 26                     |
| VH6.A11           | 118             | 6                            | VH6-35-1                   | 3                              | 3,0%                             | 122                    |
| A10               | 107             | 6                            | VH6-35-1                   | 3                              | 3,0%                             | 68                     |
| E55 6.1           | 120             | 6                            | VH6-35-1                   | 4                              | 4,0%                             | 26                     |
| FK-001            | 124             | 6                            | VH6-35-1                   | 4                              | 4,0%                             | 65                     |
| VH6.A5            | 121             | 6                            | VH6-35-1                   | 4                              | 4,0%                             | 122                    |
| VH6.A7            | 123             | 6                            | VH6-35-1                   | 4                              | 4,0%                             | 122                    |
| HBp2              | 119             | 6                            | VH6-35-1                   | 4                              | 4,0%                             | 4                      |
| Au46.2            | 123             | 6                            | VH6-35-1                   | 5                              | 5,0%                             | 49                     |
| A431              | 106             | 6                            | VH6-35-1                   | 5                              | 5,0%                             | 68                     |
| VH6.A2            | 120             | 6                            | VH6-35-1                   | 5                              | 5,0%                             | 122                    |
| VH6.A9            | 125             | 6                            | VH6-35-1                   | 8                              | 7,9%                             | 122                    |
| VH6.A8            | 118             | 6                            | VH6-35-1                   | 10                             | 9,9%                             | 122                    |
| VH6-FF3           | 118             | 6                            | VH6-35-1                   | 2                              | 2,0%                             | 123                    |
| VH6.A10           | 126             | 6                            | VH6-35-1                   | 12                             | 11,9%                            | 122                    |

Table 2C: (continued)

| Name <sup>1</sup> | aa <sup>2</sup> | Computed family <sup>3</sup> | Germline gene <sup>4</sup> | Diff. to germline <sup>5</sup> | % diff. to germline <sup>6</sup> | Reference <sup>7</sup> |
|-------------------|-----------------|------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------|
| VH6-EB10          | 117             | 6                            | VH6-35-1                   | 3                              | 3,0%                             | 123                    |
| VH6-E6            | 119             | 6                            | VH6-35-1                   | 6                              | 5,9%                             | 123                    |
| VH6-FE2           | 121             | 6                            | VH6-35-1                   | 6                              | 5,9%                             | 123                    |
| VH6-EE6           | 116             | 6                            | VH6-35-1                   | 6                              | 5,9%                             | 123                    |
| VH6-FD10          | 118             | 6                            | VH6-35-1                   | 6                              | 5,9%                             | 123                    |
| VH6-EX8           | 113             | 6                            | VH6-35-1                   | 6                              | 5,9%                             | 123                    |
| VH6-FG9           | 121             | 6                            | VH6-35-1                   | 8                              | 7,9%                             | 123                    |
| VH6-E5            | 116             | 6                            | VH6-35-1                   | 9                              | 8,9%                             | 123                    |
| VH6-EC8           | 122             | 6                            | VH6-35-1                   | 9                              | 8,9%                             | 123                    |
| VH6-E10           | 120             | 6                            | VH6-35-1                   | 10                             | 9,9%                             | 123                    |
| VH6-FF11          | 122             | 6                            | VH6-35-1                   | 11                             | 10,9%                            | 123                    |
| VH6-FD2           | 115             | 6                            | VH6-35-1                   | 11                             | 10,9%                            | 123                    |
| CLL10 17-2        | 88              | 6                            | VH6-35-1                   | 4                              | 4,0%                             | 29                     |
| VH6-BB11          | 94              | 6                            | VH6-35-1                   | 4                              | 4,0%                             | 123                    |
| VH6-B4I           | 93              | 6                            | VH6-35-1                   | 7                              | 6,9%                             | 123                    |
| JU17              | 102             | 6                            | VH6-35-1                   | 3                              | 3,0%                             | 114                    |
| VH6-BD9           | 96              | 6                            | VH6-35-1                   | 11                             | 10,9%                            | 123                    |
| VH6-BB9           | 94              | 6                            | VH6-35-1                   | 12                             | 11,9%                            | 123                    |

Table 3A: assignment of rearranged V kappa sequences to their germline counterparts

| Family <sup>1</sup> | Name   | Rearranged <sup>2</sup> | Sum         |
|---------------------|--------|-------------------------|-------------|
| 1                   | Vk1-1  | 28                      |             |
| 1                   | Vk1-2  | 0                       |             |
| 1                   | Vk1-3  | 1                       |             |
| 1                   | Vk1-4  | 0                       |             |
| 1                   | Vk1-5  | 7                       |             |
| 1                   | Vk1-6  | 0                       |             |
| 1                   | Vk1-7  | 0                       |             |
| 1                   | Vk1-8  | 2                       |             |
| 1                   | Vk1-9  | 9                       |             |
| 1                   | Vk1-10 | 0                       |             |
| 1                   | Vk1-11 | 1                       |             |
| 1                   | Vk1-12 | 7                       |             |
| 1                   | Vk1-13 | 1                       |             |
| 1                   | Vk1-14 | 7                       |             |
| 1                   | Vk1-15 | 2                       |             |
| 1                   | Vk1-16 | 2                       |             |
| 1                   | Vk1-17 | 16                      |             |
| 1                   | Vk1-18 | 1                       |             |
| 1                   | Vk1-19 | 33                      |             |
| 1                   | Vk1-20 | 1                       |             |
| 1                   | Vk1-21 | 1                       |             |
| 1                   | Vk1-22 | 0                       |             |
| 1                   | Vk1-23 | 0                       | 119 entries |
| 2                   | Vk2-1  | 0                       |             |
| 2                   | Vk2-2  | 1                       |             |
| 2                   | Vk2-3  | 0                       |             |
| 2                   | Vk2-4  | 0                       |             |
| 2                   | Vk2-5  | 0                       |             |
| 2                   | Vk2-6  | 16                      |             |
| 2                   | Vk2-7  | 0                       |             |
| 2                   | Vk2-8  | 0                       |             |
| 2                   | Vk2-9  | 1                       |             |
| 2                   | Vk2-10 | 0                       |             |
| 2                   | Vk2-11 | 7                       |             |
| 2                   | Vk2-12 | 0                       | 25 entries  |
| 3                   | Vk3-1  | 1                       |             |
| 3                   | Vk3-2  | 0                       |             |

Table 3A: (continued)

| Family <sup>1</sup> | Name  | Rearranged <sup>2</sup> | Sum                |
|---------------------|-------|-------------------------|--------------------|
| 3                   | Vk3-3 | 35                      |                    |
| 3                   | Vk3-4 | 115                     |                    |
| 3                   | Vk3-5 | 0                       |                    |
| 3                   | Vk3-6 | 0                       |                    |
| 3                   | Vk3-7 | 1                       |                    |
| 3                   | Vk3-8 | 40                      | <i>192 entries</i> |
| 4                   | Vk4-1 | 33                      | <i>33 entries</i>  |
| 5                   | Vk5-1 | 1                       | <i>1 entry</i>     |
| 6                   | Vk6-1 | 0                       |                    |
| 6                   | Vk6-2 | 0                       | <i>0 entries</i>   |
| 7                   | Vk7-1 | 0                       | <i>0 entries</i>   |

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Table 3B: assignment of rearranged V lambda sequences to their germline counterparts

| Family <sup>1</sup> | Name        | Rearranged <sup>2</sup> | Sum        |
|---------------------|-------------|-------------------------|------------|
| 1                   | DPL1        | 1                       |            |
| 1                   | DPL2        | 14                      |            |
| 1                   | DPL3        | 6                       |            |
| 1                   | DPL4        | 1                       |            |
| 1                   | HUMLV117    | 4                       |            |
| 1                   | DPL5        | 13                      |            |
| 1                   | DPL6        | 0                       |            |
| 1                   | DPL7        | 0                       |            |
| 1                   | DPL8        | 3                       |            |
| 1                   | DPL9        | 0                       | 42 entries |
| 2                   | DPL10       | 5                       |            |
| 2                   | VLAMBDA 2.1 | 0                       |            |
| 2                   | DPL11       | 23                      |            |
| 2                   | DPL12       | 15                      |            |
| 2                   | DPL13       | 0                       |            |
| 2                   | DPL14       | 0                       | 43 entries |
| 3                   | DPL16       | 10                      |            |
| 3                   | DPL23       | 19                      |            |
| 3                   | Humlv318    | 9                       | 38 entries |
| 7                   | DPL18       | 1                       |            |
| 7                   | DPL19       | 0                       | 1 entries  |
| 8                   | DPL21       | 2                       |            |
| 8                   | HUMLV801    | 6                       | 8 entries  |
| 9                   | DPL22       | 0                       | 0 entries  |
| unassigned          | DPL24       | 0                       | 0 entries  |
| 10                  | gVLX-4.4    | 0                       | 0 entries  |

Table 3C: assignment of rearranged V heavy chain sequences to their germline counterparts

| Family <sup>1</sup> | Name      | Rearranged <sup>2</sup> | Sum         |
|---------------------|-----------|-------------------------|-------------|
| 1                   | VH1-12-1  | 38                      |             |
| 1                   | VH1-12-8  | 2                       |             |
| 1                   | VH1-12-2  | 2                       |             |
| 1                   | VH1-12-9  | 2                       |             |
| 1                   | VH1-12-3  | 0                       |             |
| 1                   | VH1-12-4  | 0                       |             |
| 1                   | VH1-12-5  | 3                       |             |
| 1                   | VH1-12-6  | 0                       |             |
| 1                   | VH1-12-7  | 23                      |             |
| 1                   | VH1-13-1  | 1                       |             |
| 1                   | VH1-13-2  | 1                       |             |
| 1                   | VH1-13-3  | 0                       |             |
| 1                   | VH1-13-4  | 0                       |             |
| 1                   | VH1-13-5  | 0                       |             |
| 1                   | VH1-13-6  | 17                      |             |
| 1                   | VH1-13-7  | 0                       |             |
| 1                   | VH1-13-8  | 3                       |             |
| 1                   | VH1-13-9  | 0                       |             |
| 1                   | VH1-13-10 | 0                       |             |
| 1                   | VH1-13-11 | 0                       |             |
| 1                   | VH1-13-12 | 10                      |             |
| 1                   | VH1-13-13 | 0                       |             |
| 1                   | VH1-13-14 | 0                       |             |
| 1                   | VH1-13-15 | 4                       |             |
| 1                   | VH1-13-16 | 2                       |             |
| 1                   | VH1-13-17 | 0                       |             |
| 1                   | VH1-13-18 | 1                       |             |
| 1                   | VH1-13-19 | 0                       |             |
| 1                   | VH1-1X-1  | 1                       | 110 entries |
| 2                   | VH2-21-1  | 0                       |             |
| 2                   | VH2-31-1  | 0                       |             |
| 2                   | VH2-31-2  | 1                       |             |
| 2                   | VH2-31-3  | 1                       |             |
| 2                   | VH2-31-4  | 0                       |             |
| 2                   | VH2-31-5  | 2                       |             |
| 2                   | VH2-31-6  | 0                       |             |
| 2                   | VH2-31-7  | 0                       |             |

Table 3C: (continued)

| Family <sup>1</sup> | Name      | Rearranged <sup>2</sup> | Sum       |
|---------------------|-----------|-------------------------|-----------|
| 2                   | VH2-31-14 | 1                       |           |
| 2                   | VH2-31-8  | 0                       |           |
| 2                   | VH2-31-9  | 0                       |           |
| 2                   | VH2-31-10 | 0                       |           |
| 2                   | VH2-31-11 | 1                       |           |
| 2                   | VH2-31-12 | 0                       |           |
| 2                   | VH2-31-13 | 1                       | 7 entries |
| 3                   | VH3-11-1  | 0                       |           |
| 3                   | VH3-11-2  | 0                       |           |
| 3                   | VH3-11-3  | 5                       |           |
| 3                   | VH3-11-4  | 0                       |           |
| 3                   | VH3-11-5  | 1                       |           |
| 3                   | VH3-11-6  | 1                       |           |
| 3                   | VH3-11-7  | 0                       |           |
| 3                   | VH3-11-8  | 5                       |           |
| 3                   | VH3-13-1  | 9                       |           |
| 3                   | VH3-13-2  | 3                       |           |
| 3                   | VH3-13-3  | 0                       |           |
| 3                   | VH3-13-4  | 0                       |           |
| 3                   | VH3-13-5  | 0                       |           |
| 3                   | VH3-13-6  | 0                       |           |
| 3                   | VH3-13-7  | 32                      |           |
| 3                   | VH3-13-8  | 4                       |           |
| 3                   | VH3-13-9  | 0                       |           |
| 3                   | VH3-13-10 | 46                      |           |
| 3                   | VH3-13-11 | 0                       |           |
| 3                   | VH3-13-12 | 11                      |           |
| 3                   | VH3-13-13 | 17                      |           |
| 3                   | VH3-13-14 | 8                       |           |
| 3                   | VH3-13-15 | 4                       |           |
| 3                   | VH3-13-16 | 3                       |           |
| 3                   | VH3-13-17 | 2                       |           |
| 3                   | VH3-13-18 | 1                       |           |
| 3                   | VH3-13-19 | 13                      |           |
| 3                   | VH3-13-20 | 1                       |           |
| 3                   | VH3-13-21 | 1                       |           |
| 3                   | VH3-13-22 | 0                       |           |

Table 3C: (continued)

| Family <sup>1</sup> | Name      | Rearranged <sup>2</sup> | Sum         |
|---------------------|-----------|-------------------------|-------------|
| 3                   | VH3-13-23 | 0                       |             |
| 3                   | VH3-13-24 | 4                       |             |
| 3                   | VH3-13-25 | 1                       |             |
| 3                   | VH3-13-26 | 6                       |             |
| 3                   | VH3-14-1  | 1                       |             |
| 3                   | VH3-14-4  | 15                      |             |
| 3                   | VH3-14-2  | 0                       |             |
| 3                   | VH3-14-3  | 0                       |             |
| 3                   | VH3-1X-1  | 0                       |             |
| 3                   | VH3-1X-2  | 0                       |             |
| 3                   | VH3-1X-3  | 6                       |             |
| 3                   | VH3-1X-4  | 0                       |             |
| 3                   | VH3-1X-5  | 0                       |             |
| 3                   | VH3-1X-6  | 11                      |             |
| 3                   | VH3-1X-7  | 0                       |             |
| 3                   | VH3-1X-8  | 1                       |             |
| 3                   | VH3-1X-9  | 0                       | 212 entries |
| 4                   | VH4-11-1  | 0                       |             |
| 4                   | VH4-11-2  | 20                      |             |
| 4                   | VH4-11-3  | 0                       |             |
| 4                   | VH4-11-4  | 0                       |             |
| 4                   | VH4-11-5  | 0                       |             |
| 4                   | VH4-11-6  | 0                       |             |
| 4                   | VH4-11-7  | 5                       |             |
| 4                   | VH4-11-8  | 7                       |             |
| 4                   | VH4-11-9  | 3                       |             |
| 4                   | VH4-11-10 | 0                       |             |
| 4                   | VH4-11-11 | 0                       |             |
| 4                   | VH4-11-12 | 4                       |             |
| 4                   | VH4-11-13 | 0                       |             |
| 4                   | VH4-11-14 | 0                       |             |
| 4                   | VH4-11-15 | 0                       |             |
| 4                   | VH4-11-16 | 1                       |             |
| 4                   | VH4-21-1  | 0                       |             |
| 4                   | VH4-21-2  | 0                       |             |
| 4                   | VH4-21-3  | 1                       |             |
| 4                   | VH4-21-4  | 1                       |             |



Table 3C: (continued)

| Family <sup>1</sup> | Name      | Rearranged <sup>2</sup> | Sum        |
|---------------------|-----------|-------------------------|------------|
| 4                   | VH4-21-5  | 1                       |            |
| 4                   | VH4-21-6  | 1                       |            |
| 4                   | VH4-21-7  | 0                       |            |
| 4                   | VH4-21-8  | 0                       |            |
| 4                   | VH4-21-9  | 0                       |            |
| 4                   | VH4-31-1  | 0                       |            |
| 4                   | VH4-31-2  | 0                       |            |
| 4                   | VH4-31-3  | 0                       |            |
| 4                   | VH4-31-4  | 2                       |            |
| 4                   | VH4-31-5  | 0                       |            |
| 4                   | VH4-31-6  | 0                       |            |
| 4                   | VH4-31-7  | 0                       |            |
| 4                   | VH4-31-8  | 0                       |            |
| 4                   | VH4-31-9  | 0                       |            |
| 4                   | VH4-31-10 | 0                       |            |
| 4                   | VH4-31-11 | 0                       |            |
| 4                   | VH4-31-12 | 4                       |            |
| 4                   | VH4-31-13 | 7                       |            |
| 4                   | VH4-31-14 | 0                       |            |
| 4                   | VH4-31-15 | 0                       |            |
| 4                   | VH4-31-16 | 0                       |            |
| 4                   | VH4-31-17 | 0                       |            |
| 4                   | VH4-31-18 | 0                       |            |
| 4                   | VH4-31-19 | 0                       |            |
| 4                   | VH4-31-20 | 0                       | 57 entries |
| 5                   | VH5-12-1  | 82                      |            |
| 5                   | VH5-12-2  | 1                       |            |
| 5                   | VH5-12-3  | 0                       |            |
| 5                   | VH5-12-4  | 14                      | 97 entries |
| 6                   | VH6-35-1  | 74                      | 74 entries |

Table 4A: Analysis of V kappa subgroup 1

| amino acid <sup>1</sup>   | Framework I |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
|---------------------------|-------------|-----|-----|-----|------|-----|------|------|-----|-----|-----|-----|-----|-----|-----|------|
|                           | 1           | 2   | 3   | 4   | 5    | 6   | 7    | 8    | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16   |
| A                         |             | 1   |     |     |      |     |      |      | 1   |     |     | 102 |     |     | 1   |      |
| B                         |             |     | 1   |     |      | 1   |      |      |     |     |     |     |     |     |     |      |
| C                         |             |     |     |     |      |     |      |      |     |     |     |     |     | 1   |     |      |
| D                         | 64          |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| E                         | 8           | 14  |     |     |      |     |      |      |     |     |     |     |     |     | 1   |      |
| F                         |             |     |     |     |      |     |      |      | 1   | 6   |     |     |     | 1   |     |      |
| G                         |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     | 105  |
| H                         |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| I                         |             | 65  |     |     |      |     |      |      |     |     |     |     |     |     | 4   |      |
| K                         |             |     | 1   |     |      |     |      |      |     |     |     |     |     |     |     |      |
| L                         |             | 6   |     | 21  |      |     |      |      |     |     | 96  |     | 1   |     |     |      |
| M                         | 1           |     |     | 66  |      |     |      |      |     |     |     |     |     |     |     |      |
| N                         |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| P                         |             |     |     |     |      |     |      | 103  |     | 1   |     | 2   |     |     | 1   |      |
| Q                         |             |     | 62  |     |      | 88  |      |      |     |     | 1   |     |     |     |     |      |
| R                         |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| S                         |             |     |     |     |      |     | 89   |      | 102 | 80  |     | 103 |     | 103 |     |      |
| T                         |             | 1   |     |     | 88   |     |      |      |     | 18  |     |     |     |     |     |      |
| V                         |             | 1   | 9   |     |      |     |      |      |     |     | 8   |     | 2   |     | 98  |      |
| W                         |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| X                         | 1           |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| Y                         |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| -                         |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| unknown (?)               |             |     |     |     |      |     |      |      |     |     |     |     |     |     |     |      |
| not sequenced             | 31          | 31  | 18  | 18  | 17   | 16  | 16   | 2    | 1   |     |     |     |     |     |     |      |
| sum of seq <sup>2</sup>   | 74          | 74  | 87  | 87  | 88   | 89  | 89   | 103  | 104 | 105 | 105 | 105 | 105 | 105 | 105 | 105  |
| oomcaa <sup>3</sup>       | 64          | 65  | 62  | 66  | 88   | 88  | 89   | 103  | 102 | 80  | 96  | 103 | 102 | 103 | 98  | 105  |
| mcaa <sup>4</sup>         | D           | I   | Q   | M   | T    | Q   | S    | P    | S   | S   | L   | S   | A   | S   | V   | G    |
| rel. oomcaa <sup>5</sup>  | 86%         | 88% | 71% | 76% | 100% | 99% | 100% | 100% | 98% | 76% | 91% | 98% | 97% | 98% | 93% | 100% |
| pos occupied <sup>6</sup> | 4           | 5   | 5   | 2   | 1    | 2   | 1    | 1    | 3   | 4   | 3   | 2   | 3   | 3   | 5   | 1    |

Table 4A: Analysis of V kappa subgroup 1

| amino acid <sup>1</sup>    | 17  | 18  | 19  | 20  | 21  | 22  | 23   | 24  | 25  | 26  | 27  | A    | B    | C    | D    |
|----------------------------|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|------|------|------|
| A                          |     |     | 1   | 1   |     | 1   |      |     | 103 |     |     |      |      |      |      |
| B                          |     |     |     |     |     |     |      |     |     |     | 1   |      |      |      |      |
| C                          |     |     |     |     |     |     | 105  |     |     |     |     |      |      |      |      |
| D                          | 101 |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| E                          | 2   |     |     |     |     |     |      | 1   | 1   |     | 2   |      |      |      |      |
| F                          |     |     |     |     | 2   |     |      |     |     |     |     |      |      |      |      |
| G                          |     |     |     |     |     |     |      |     |     | 1   |     |      |      |      |      |
| H                          |     |     |     |     |     |     |      |     |     |     | 1   |      |      |      |      |
| I                          |     |     | 6   | 4   | 101 | 1   |      |     |     |     |     |      |      |      |      |
| K                          |     |     |     |     |     |     |      | 2   |     |     | 1   |      |      |      |      |
| L                          |     |     |     |     |     |     |      | 1   |     |     |     |      |      |      |      |
| M                          |     |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| N                          |     |     |     |     |     |     |      |     |     | 1   |     |      |      |      |      |
| P                          |     |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| Q                          |     |     |     |     |     |     |      | 20  |     |     | 100 |      |      |      |      |
| R                          |     | 94  |     |     |     |     |      | 81  |     |     |     |      |      |      |      |
| S                          |     | 5   |     | 1   |     |     |      |     |     | 102 |     |      |      |      |      |
| T                          |     | 6   |     | 99  |     | 103 |      |     | 1   | 1   |     |      |      |      |      |
| V                          |     |     | 98  |     | 2   |     |      |     |     |     |     |      |      |      |      |
| W                          |     |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| X                          | 1   |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| Y                          | 1   |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| -                          |     |     |     |     |     |     |      |     |     |     |     | 105  | 105  | 105  | 105  |
| unknown (?)                |     |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| not sequenced <sup>2</sup> |     |     |     |     |     |     |      |     |     |     |     |      |      |      |      |
| sum of seq <sup>2</sup>    | 105 | 105 | 105 | 105 | 105 | 105 | 105  | 105 | 105 | 105 | 105 | 105  | 105  | 105  | 105  |
| oomcaa <sup>3</sup>        | 101 | 94  | 98  | 99  | 101 | 103 | 105  | 81  | 103 | 102 | 100 | 105  | 105  | 105  | 105  |
| mcaa <sup>4</sup>          | D   | R   | V   | T   | I   | T   | C    | R   | A   | S   | Q   | -    | -    | -    | -    |
| rel. oomcaa <sup>5</sup>   | 96% | 90% | 93% | 94% | 96% | 98% | 100% | 77% | 98% | 97% | 95% | 100% | 100% | 100% | 100% |
| pos occupied <sup>6</sup>  | 4   | 3   | 3   | 4   | 3   | 3   | 1    | 5   | 3   | 4   | 5   | 1    | 1    | 1    | 1    |

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Table 4A: Analysis of V kappa subgroup 1

|                           | CDRI |      |     |     |     |     |     |     |     |      |     |     |     |     |     |  |
|---------------------------|------|------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|--|
| amino acid <sup>1</sup>   | E    | F    | 28  | 29  | 30  | 31  | 32  | 33  | 34  | 35   | 36  | 37  | 38  | 39  | 40  |  |
| A                         |      |      |     |     | 1   | 1   |     | 1   | 42  |      |     |     |     |     |     |  |
| B                         |      |      |     |     |     |     |     |     |     |      |     | 1   | 1   |     |     |  |
| C                         |      |      |     |     |     |     | 1   |     |     |      |     |     |     |     |     |  |
| D                         |      |      | 25  |     | 1   | 5   | 7   |     |     |      |     | 1   |     |     |     |  |
| E                         |      |      |     |     |     |     | 1   |     |     |      |     | 2   |     |     |     |  |
| F                         |      |      |     | 1   | 1   |     | 7   |     |     |      | 6   |     |     |     |     |  |
| G                         |      |      | 25  |     | 7   | 3   |     |     | 4   |      |     |     |     |     |     |  |
| H                         |      |      |     |     | 1   | 2   | 2   |     | 1   |      |     | 2   |     |     |     |  |
| I                         |      |      |     | 98  | 1   | 4   |     |     | 1   |      |     |     |     |     |     |  |
| K                         |      |      |     |     |     | 7   |     |     |     |      |     |     |     | 95  |     |  |
| L                         |      |      |     |     | 2   | 1   |     | 101 |     |      |     |     |     |     |     |  |
| M                         |      |      |     |     |     |     |     |     |     |      |     |     |     |     |     |  |
| N                         |      |      | 6   |     | 16  | 42  |     |     | 50  |      |     |     |     |     |     |  |
| P                         |      |      |     |     |     |     |     |     |     |      |     |     |     |     | 102 |  |
| Q                         |      |      |     |     |     |     |     |     |     |      |     | 98  | 103 | 2   |     |  |
| R                         |      |      |     |     | 16  | 3   | 2   |     |     |      |     |     |     | 3   | 1   |  |
| S                         |      |      | 41  | 2   | 57  | 32  | 3   | 1   | 1   |      |     |     |     |     | 1   |  |
| T                         |      |      | 7   |     |     | 4   |     |     | 4   |      |     |     |     | 1   |     |  |
| V                         |      |      | 1   | 4   | 1   |     |     | 1   |     |      |     |     |     |     |     |  |
| W                         |      |      |     |     |     |     | 21  |     |     | 104  |     |     |     |     |     |  |
| X                         |      |      |     |     |     |     |     |     | 1   |      |     |     |     |     |     |  |
| Y                         |      |      |     |     | 1   |     | 60  |     |     |      | 98  |     |     |     |     |  |
| -                         | 105  | 105  |     |     |     |     |     |     |     |      |     |     |     |     |     |  |
| unknown (?)               |      |      |     |     |     |     |     |     |     |      |     |     |     | 3   |     |  |
| not sequenced             |      |      |     |     |     | 1   | 1   | 1   | 1   | 1    | 1   | 1   | 1   | 1   | 1   |  |
| sum of seq <sup>2</sup>   | 105  | 105  | 105 | 105 | 105 | 104 | 104 | 104 | 104 | 104  | 104 | 104 | 104 | 104 | 104 |  |
| oomcaa <sup>3</sup>       | 105  | 105  | 41  | 98  | 57  | 42  | 60  | 101 | 50  | 104  | 98  | 98  | 103 | 95  | 102 |  |
| mcaa <sup>4</sup>         | -    | -    | S   | I   | S   | N   | Y   | L   | N   | W    | Y   | Q   | Q   | K   | P   |  |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 39% | 93% | 54% | 40% | 58% | 97% | 48% | 100% | 94% | 94% | 99% | 91% | 98% |  |
| pos occupied <sup>6</sup> | 1    | 1    | 6   | 4   | 12  | 11  | 9   | 4   | 8   | 1    | 2   | 5   | 2   | 4   | 3   |  |

3+

Table 4A: Analysis of V kappa subgroup 1

| amino acid <sup>1</sup>   | Framework II |     |     |      |     |     |      |     |     | CDR II |     |     |     |     |     |
|---------------------------|--------------|-----|-----|------|-----|-----|------|-----|-----|--------|-----|-----|-----|-----|-----|
|                           | 41           | 42  | 43  | 44   | 45  | 46  | 47   | 48  | 49  | 50     | 51  | 52  | 53  | 54  | 55  |
| A                         |              |     | 94  |      |     |     |      |     |     | 50     | 95  |     |     |     |     |
| B                         |              |     |     |      |     |     |      |     |     |        |     |     |     |     |     |
| C                         |              |     |     |      |     |     |      |     |     |        |     |     |     |     |     |
| D                         |              |     |     |      |     |     |      |     |     | 21     | 1   | 1   | 1   |     |     |
| E                         | 1            | 3   |     |      | 1   | 1   |      |     |     | 1      |     | 1   |     |     | 33  |
| F                         |              |     |     |      |     | 1   |      |     | 3   |        |     | 1   |     |     |     |
| G                         | 100          |     | 1   |      |     |     |      |     |     | 9      | 2   |     |     |     |     |
| H                         |              |     |     |      |     |     |      |     | 2   |        |     |     |     |     | 1   |
| I                         |              | 1   |     |      |     | 1   |      | 100 |     |        |     |     | 1   |     |     |
| K                         |              | 95  |     |      | 86  |     |      |     |     | 16     |     |     | 2   |     | 5   |
| L                         |              | 1   |     |      |     | 89  | 103  |     |     |        |     |     |     | 101 |     |
| M                         |              |     |     |      |     |     |      | 2   |     |        |     |     |     |     |     |
| N                         |              |     |     |      | 10  |     |      |     |     | 2      |     | 1   | 25  |     |     |
| P                         |              |     |     | 104  |     |     |      |     |     | 1      |     |     |     |     | 1   |
| Q                         |              | 1   |     |      | 1   |     |      |     |     |        |     |     |     |     | 62  |
| R                         |              |     |     |      | 3   | 3   |      |     |     |        |     |     | 1   | 1   | 2   |
| S                         |              |     |     |      | 1   |     |      |     | 5   | 1      | 1   | 99  | 41  | 2   |     |
| T                         |              | 3   |     |      | 1   |     |      |     |     | 1      | 4   | 1   | 31  |     |     |
| V                         |              |     | 9   |      |     | 9   |      |     |     |        | 1   |     | 1   |     |     |
| W                         |              |     |     |      |     |     |      |     |     |        |     |     |     | 1   |     |
| X                         |              |     |     |      | 1   |     |      |     |     |        |     |     |     |     |     |
| Y                         |              |     |     |      |     |     |      |     | 92  | 1      |     |     |     |     |     |
| -                         |              |     |     |      |     |     |      |     |     |        |     |     |     |     |     |
| unknown (?)               | 3            |     |     |      |     |     |      |     |     |        |     |     |     |     |     |
| not sequenced             | 1            | 1   | 1   | 1    | 1   | 1   | 1    | 2   | 3   | 3      | 2   | 1   | 1   | 1   | 1   |
| sum of seq <sup>2</sup>   | 104          | 104 | 104 | 104  | 104 | 104 | 103  | 102 | 102 | 103    | 104 | 104 | 104 | 104 | 104 |
| oomcaa <sup>3</sup>       | 100          | 95  | 94  | 104  | 86  | 89  | 103  | 100 | 92  | 50     | 95  | 99  | 41  | 101 | 62  |
| mcaa <sup>4</sup>         | G            | K   | A   | P    | K   | L   | L    | I   | Y   | A      | A   | S   | S   | L   | Q   |
| rel. oomcaa <sup>5</sup>  | 96%          | 91% | 90% | 100% | 83% | 86% | 100% | 98% | 90% | 49%    | 91% | 95% | 39% | 97% | 60% |
| pos occupied <sup>6</sup> | 2            | 6   | 3   | 1    | 8   | 6   | 1    | 2   | 4   | 10     | 6   | 6   | 9   | 3   | 6   |

Table 4A: Analysis of V kappa subgroup 1

| amino acid <sup>1</sup>   | 56  | 57   | 58  | 59  | 60  | 61  | 62  | 63  | 64   | 65  | 66  | 67  | 68  | 69  | 70  |
|---------------------------|-----|------|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|
| A                         | 3   |      |     |     |     |     |     |     |      |     | 2   | 1   | 1   | 1   |     |
| B                         |     |      |     | 1   |     |     |     |     |      |     |     |     |     |     |     |
| C                         |     |      |     |     |     |     |     |     |      |     |     |     |     |     |     |
| D                         | 1   |      |     |     |     |     |     |     |      |     |     |     |     |     | 67  |
| E                         |     |      |     |     |     |     |     |     |      |     |     |     | 1   |     | 30  |
| F                         |     |      | 1   |     |     |     | 103 |     |      |     |     | 3   |     |     |     |
| G                         | 2   | 105  |     |     |     |     |     |     | 105  | 4   | 101 |     | 102 |     |     |
| H                         |     |      |     |     |     |     |     |     |      |     |     |     |     |     | 3   |
| I                         | 3   |      | 4   |     |     |     | 1   | 3   |      |     |     |     |     |     |     |
| K                         | 1   |      |     |     |     | 1   |     |     |      |     |     |     |     |     | 1   |
| L                         |     |      |     |     |     |     |     | 1   |      |     |     |     |     |     |     |
| M                         |     |      |     |     |     |     |     |     |      |     |     |     |     | 1   |     |
| N                         | 6   |      |     |     |     |     |     |     |      |     |     |     |     |     |     |
| P                         | 1   |      |     | 101 | 2   |     |     |     |      |     |     |     |     |     |     |
| Q                         |     |      |     |     |     |     |     |     |      | 1   |     |     |     |     |     |
| R                         | 1   |      |     |     |     | 103 |     | 1   |      | 1   | 1   |     |     | 2   |     |
| S                         | 68  |      |     | 2   | 103 |     |     | 98  |      | 96  |     | 100 |     |     |     |
| T                         | 19  |      |     | 1   |     | 1   |     | 2   |      | 3   |     |     |     | 101 |     |
| V                         |     |      | 99  |     |     |     | 1   |     |      |     |     |     |     |     | 1   |
| W                         |     |      |     |     |     |     |     |     |      |     |     |     |     |     |     |
| X                         |     |      | 1   |     |     |     |     |     |      |     | 1   |     | 1   |     | 2   |
| Y                         |     |      |     |     |     |     |     |     |      |     |     | 1   |     |     | 1   |
| -                         |     |      |     |     |     |     |     |     |      |     |     |     |     |     |     |
| unknown (?)               |     |      |     |     |     |     |     |     |      |     |     |     |     |     |     |
| not sequenced             |     |      |     |     |     |     |     |     |      |     |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 105 | 105  | 105 | 105 | 105 | 105 | 105 | 105 | 105  | 105 | 105 | 105 | 105 | 105 | 105 |
| oomcaa <sup>3</sup>       | 68  | 105  | 99  | 101 | 103 | 103 | 103 | 98  | 105  | 96  | 101 | 100 | 102 | 101 | 67  |
| mcaa <sup>4</sup>         | S   | G    | V   | P   | S   | R   | F   | S   | G    | S   | G   | S   | G   | T   | D   |
| rel. oomcaa <sup>5</sup>  | 65% | 100% | 94% | 96% | 98% | 98% | 98% | 93% | 100% | 91% | 96% | 95% | 97% | 96% | 64% |
| pos occupied <sup>6</sup> | 10  | 1    | 4   | 4   | 2   | 3   | 3   | 5   | 1    | 5   | 4   | 4   | 4   | 4   | 7   |

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Table 4A: Analysis of V kappa subgroup 1

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 71            | 72  | 73  | 74  | 75  | 76  | 77  | 78  | 79  | 80  | 81  | 82  | 83  | 84  | 85  |
| A                         |               | 3   |     |     |     | 1   |     |     |     | 2   |     |     |     | 101 | 1   |
| B                         |               |     |     |     | 1   |     |     |     | 3   |     | 2   |     |     |     |     |
| C                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| D                         |               |     |     |     |     | 1   |     |     |     |     | 16  | 101 |     |     |     |
| E                         |               |     |     |     |     |     |     |     |     |     | 83  |     |     |     |     |
| F                         | 102           | 1   | 21  |     |     |     |     |     |     |     |     |     | 73  |     |     |
| G                         |               |     |     |     |     |     | 4   |     |     |     | 1   |     |     | 2   |     |
| H                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| I                         |               |     |     |     | 99  | 5   |     |     |     |     |     |     | 17  |     |     |
| K                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| L                         |               |     | 81  |     |     |     |     | 103 | 1   |     |     |     | 1   |     |     |
| M                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     | 1   |
| N                         |               |     |     |     |     | 7   | 4   |     |     |     |     |     |     |     | 1   |
| P                         |               |     |     |     |     |     |     |     |     | 97  |     |     |     |     | 1   |
| Q                         |               |     |     |     |     |     |     |     | 97  |     |     |     |     |     |     |
| R                         |               |     |     |     |     | 2   | 1   |     | 2   |     |     |     |     |     |     |
| S                         |               | 2   |     | 1   |     | 86  | 94  |     |     | 4   |     |     | 1   |     |     |
| T                         |               | 98  |     | 102 |     | 2   | 1   |     |     |     |     |     |     |     | 97  |
| V                         | 1             |     | 2   |     | 4   |     |     | 1   |     |     |     |     | 11  |     | 1   |
| W                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| X                         |               |     |     | 1   |     |     |     |     |     |     | 1   | 2   |     |     |     |
| Y                         | 1             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| unknown (?)               |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| not sequenced             | 1             | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 2   | 2   | 2   | 2   | 2   | 3   |
| sum of seq <sup>2</sup>   | 104           | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 103 | 103 | 103 | 103 | 103 | 103 | 102 |
| oomcaa <sup>3</sup>       | 102           | 98  | 81  | 102 | 99  | 86  | 94  | 103 | 97  | 97  | 83  | 101 | 73  | 101 | 97  |
| mcaa <sup>4</sup>         | F             | T   | L   | T   | I   | S   | S   | L   | Q   | P   | E   | D   | F   | A   | T   |
| rel. oomcaa <sup>5</sup>  | 98%           | 94% | 78% | 98% | 95% | 83% | 90% | 99% | 94% | 94% | 81% | 98% | 71% | 98% | 95% |
| pos occupied <sup>6</sup> | 3             | 4   | 3   | 3   | 3   | 7   | 5   | 2   | 4   | 3   | 5   | 2   | 5   | 2   | 6   |

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Table 4A: Analysis of V kappa subgroup 1

| amino acid <sup>1</sup>   | CDR III |     |      |     |     |     |     |     |     |     |     |     |      |      |      |      |
|---------------------------|---------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
|                           | 86      | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B   | C    | D    | E    | F    |
| A                         |         |     |      |     | 1   | 7   | 1   |     | 5   | 1   |     |     |      |      |      |      |
| B                         |         |     |      | 2   | 3   |     |     |     |     |     |     |     |      |      |      |      |
| C                         |         |     | 102  |     |     |     |     |     |     |     |     |     |      |      |      |      |
| D                         |         |     |      |     |     |     | 23  | 5   | 1   |     |     |     |      |      |      |      |
| E                         |         |     |      |     |     |     | 1   | 1   |     | 1   | 1   |     |      |      |      |      |
| F                         |         | 7   |      |     |     | 3   |     |     | 13  |     |     |     |      |      |      |      |
| G                         |         |     |      |     |     | 1   |     | 1   | 2   | 1   |     | 1   |      |      |      |      |
| H                         |         | 1   |      | 4   | 6   | 7   | 3   | 1   |     |     |     |     |      |      |      |      |
| I                         |         |     |      |     |     |     | 4   | 1   | 2   | 1   |     |     |      |      |      |      |
| K                         | 1       |     |      |     | 7   |     | 1   |     |     |     |     |     |      |      |      |      |
| L                         |         |     |      | 7   |     | 6   | 2   |     | 18  | 2   |     |     |      |      |      |      |
| M                         |         |     |      |     |     |     |     |     |     |     |     |     |      |      |      |      |
| N                         |         |     |      |     |     | 6   | 31  | 19  | 1   |     |     |     |      |      |      |      |
| P                         |         |     |      |     |     |     |     |     | 1   | 82  | 6   |     |      |      |      |      |
| Q                         |         |     |      | 90  | 86  | 1   | 2   |     |     |     |     |     |      |      |      |      |
| R                         |         |     |      |     |     | 1   |     | 2   | 2   |     |     |     |      |      |      |      |
| S                         | 1       |     |      |     |     | 27  | 3   | 58  | 5   | 10  |     |     |      |      |      |      |
| T                         |         |     |      |     |     | 3   | 1   | 15  | 25  |     |     |     |      |      |      |      |
| V                         |         |     |      |     |     |     |     |     | 5   |     |     |     |      |      |      |      |
| W                         |         |     |      |     |     |     |     |     | 1   |     |     |     |      |      |      |      |
| X                         |         |     |      |     |     |     |     |     |     |     |     |     |      |      |      |      |
| Y                         | 101     | 93  |      |     |     | 42  | 32  | 1   | 23  |     |     |     |      |      |      |      |
| -                         |         |     |      |     |     |     |     |     |     | 3   | 82  | 88  | 89   | 89   | 89   | 89   |
| unknown (?)               |         | 1   |      |     |     |     |     |     |     |     |     |     |      |      |      |      |
| not sequenced             | 2       | 3   | 3    | 2   | 2   | 1   | 1   | 1   | 1   | 4   | 16  | 16  | 16   | 16   | 16   | 16   |
| sum of seq <sup>2</sup>   | 103     | 102 | 102  | 103 | 103 | 104 | 104 | 104 | 104 | 101 | 89  | 89  | 89   | 89   | 89   | 89   |
| oomcaa <sup>3</sup>       | 101     | 93  | 102  | 90  | 86  | 42  | 32  | 58  | 25  | 82  | 82  | 88  | 89   | 89   | 89   | 89   |
| mcaa <sup>4</sup>         | Y       | Y   | C    | Q   | Q   | Y   | Y   | S   | T   | P   | -   | -   | -    | -    | -    | -    |
| rel. oomcaa <sup>5</sup>  | 98%     | 91% | 100% | 87% | 83% | 40% | 31% | 56% | 24% | 81% | 92% | 99% | 100% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 3       | 3   | 1    | 4   | 5   | 11  | 12  | 10  | 14  | 8   | 3   | 2   | 1    | 1    | 1    | 1    |

90



Table 4A: Analysis of V kappa subgroup 1

| amino acid <sup>1</sup>   | Framework IV |     |     |      |     |      |      |     |     |     |     |      |     | sum |      |
|---------------------------|--------------|-----|-----|------|-----|------|------|-----|-----|-----|-----|------|-----|-----|------|
|                           | 96           | 97  | 98  | 99   | 100 | 101  | 102  | 103 | 104 | 105 | 106 | A    | 107 |     | 108  |
| A                         | 1            |     |     |      |     |      |      |     |     |     |     |      |     |     | 627  |
| B                         |              |     |     |      | 1   |      |      |     |     | 1   |     |      |     |     | 19   |
| C                         |              |     |     |      |     |      |      |     |     |     |     |      |     |     | 209  |
| D                         | 1            |     |     |      |     |      |      |     |     | 15  |     |      |     |     | 459  |
| E                         |              |     |     |      | 2   |      |      |     |     | 65  |     |      |     |     | 258  |
| F                         | 6            |     | 86  |      |     |      |      |     |     |     | 2   |      |     |     | 451  |
| G                         |              |     |     | 87   | 29  | 87   |      |     |     |     |     |      |     | 2   | 894  |
| H                         | 2            | 1   |     |      |     |      |      |     |     |     |     |      |     |     | 40   |
| I                         | 5            |     |     |      |     |      |      |     | 1   |     | 72  |      |     |     | 606  |
| K                         | 1            | 1   |     |      |     |      |      | 77  |     |     |     |      | 79  |     | 480  |
| L                         | 18           | 1   | 1   |      |     |      |      |     | 22  | 4   | 2   |      |     |     | 793  |
| M                         |              | 1   |     |      |     |      |      |     |     |     | 5   |      |     |     | 77   |
| N                         | 1            |     |     |      |     |      |      |     |     |     | 1   |      | 2   |     | 232  |
| P                         | 6            |     |     |      | 7   |      |      |     |     |     |     |      |     | 1   | 620  |
| Q                         | 1            |     |     |      | 48  |      |      |     |     |     | 1   |      |     |     | 865  |
| R                         | 6            |     |     |      |     |      |      | 6   |     |     |     |      | 2   | 70  | 413  |
| S                         | 2            | 2   |     |      |     |      |      |     |     |     |     |      |     |     | 1636 |
| T                         | 2            | 82  |     |      |     |      | 87   | 3   |     |     |     |      | 2   |     | 1021 |
| V                         | 2            |     |     |      |     |      |      | 1   | 63  |     | 3   |      |     |     | 440  |
| W                         | 15           |     |     |      |     |      |      |     |     |     |     |      |     |     | 141  |
| X                         |              |     |     |      |     |      |      |     |     |     |     |      |     |     | 14   |
| Y                         | 16           |     |     |      |     |      |      |     |     |     |     |      |     |     | 564  |
| -                         | 4            | 1   |     |      |     |      |      |     |     |     |     | 85   |     | 1   | 1250 |
| unknown (?)               |              |     |     |      |     |      |      |     |     |     |     |      |     |     | 7    |
| not sequenced             | 16           | 16  | 18  | 18   | 18  | 18   | 18   | 18  | 19  | 19  | 20  | 20   | 20  | 31  | 589  |
| sum of seq <sup>2</sup>   | 89           | 89  | 87  | 87   | 87  | 87   | 87   | 87  | 86  | 86  | 85  | 85   | 85  | 74  |      |
| oomcaa <sup>3</sup>       | 18           | 82  | 86  | 87   | 48  | 87   | 87   | 77  | 63  | 65  | 72  | 85   | 79  | 70  |      |
| mcaa <sup>4</sup>         | L            | T   | F   | G    | G   | G    | T    | K   | V   | E   | I   | -    | K   | R   |      |
| rel. oomcaa <sup>5</sup>  | 20%          | 92% | 99% | 100% | 55% | 100% | 100% | 89% | 73% | 76% | 85% | 100% | 93% | 95% |      |
| pos occupied <sup>6</sup> | 17           | 7   | 2   | 1    | 5   | 1    | 1    | 4   | 3   | 5   | 6   | 1    | 4   | 4   |      |

99

Table 4B: Analysis of V kappa subgroup 2

| Framework I               |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
|---------------------------|-----|-----|------|-----|-----|------|------|------|-----|-----|------|------|------|------|-----|------|-----|------|------|------|----|
| amino acid <sup>1</sup>   | 1   | 2   | 3    | 4   | 5   | 6    | 7    | 8    | 9   | 10  | 11   | 12   | 13   | 14   | 15  | 16   | 17  | 18   | 19   | 20   | 21 |
| A                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      | 22   |      |    |
| B                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| C                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| D                         | 14  |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| E                         | 3   |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      | 15  |      |      |      |    |
| F                         |     |     |      |     |     |      |      |      | 1   | 1   |      |      |      |      |     |      |     |      |      |      |    |
| G                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     | 22   |     |      |      |      |    |
| H                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| I                         |     | 8   |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      | 22   |    |
| K                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| L                         |     | 3   |      | 1   |     |      |      |      | 17  | 18  |      |      |      |      | 6   |      |     |      |      |      |    |
| M                         |     |     |      | 15  |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| N                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| P                         |     |     |      |     |     |      |      | 18   |     |     |      | 18   |      |      | 15  |      | 22  |      |      |      |    |
| Q                         |     |     |      |     |     | 18   |      |      |     |     |      |      |      |      |     |      | 7   |      |      |      |    |
| R                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| S                         |     |     |      |     |     |      | 18   |      |     | 17  |      |      |      |      |     |      |     |      |      | 22   |    |
| T                         |     |     |      | 17  |     |      |      |      |     |     |      |      |      | 21   |     |      |     |      |      |      |    |
| V                         |     | 6   | 17   | 1   |     |      |      |      |     |     |      |      | 18   |      |     |      |     |      |      |      |    |
| W                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| X                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| Y                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| -                         |     |     |      |     |     |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| unknown (?)               |     |     |      |     | 1   |      |      |      |     |     |      |      |      |      |     |      |     |      |      |      |    |
| not sequenced             | 5   | 5   | 5    | 5   | 4   | 4    | 4    | 4    | 4   | 4   | 4    | 4    | 4    | 1    | 1   |      |     |      |      |      |    |
| sum of seq <sup>2</sup>   | 17  | 17  | 17   | 17  | 18  | 18   | 18   | 18   | 18  | 18  | 18   | 18   | 18   | 21   | 21  | 22   | 22  | 22   | 22   | 22   |    |
| oomcaa <sup>3</sup>       | 14  | 8   | 17   | 15  | 17  | 18   | 18   | 18   | 17  | 17  | 18   | 18   | 18   | 21   | 15  | 22   | 15  | 22   | 22   | 22   |    |
| mcaa <sup>4</sup>         | D   | I   | V    | M   | T   | Q    | S    | P    | L   | S   | L    | P    | V    | T    | P   | G    | E   | P    | A    | S    |    |
| rel. oomcaa <sup>5</sup>  | 82% | 47% | 100% | 88% | 94% | 100% | 100% | 100% | 94% | 94% | 100% | 100% | 100% | 100% | 71% | 100% | 68% | 100% | 100% | 100% |    |
| pos occupied <sup>6</sup> | 2   | 3   | 1    | 3   | 1   | 1    | 1    | 1    | 2   | 2   | 1    | 1    | 1    | 1    | 2   | 1    | 2   | 1    | 1    | 1    |    |

Table 4B: Analysis of V kappa subgroup 2

| amino acid <sup>1</sup>   | CDRI |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
|---------------------------|------|------|-----|------|------|-----|------|------|-----|-----|-----|------|-----|------|-----|-----|-----|------|-----|------|-----|----|----|----|----|----|
|                           | 22   | 23   | 24  | 25   | 26   | 27  | A    | B    | C   | D   | E   | F    | 28  | 29   | 30  | 31  | 32  | 33   | 34  | 35   | 36  |    |    |    |    |    |
| A                         |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| B                         |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| C                         |      | 22   |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| D                         |      |      |     |      |      |     |      |      |     | 1   |     |      | 9   |      | 1   | 1   |     |      | 11  |      |     |    |    |    |    |    |
| E                         |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| F                         |      |      |     |      |      |     |      |      |     |     |     |      |     |      | 2   |     |     |      |     |      |     |    |    |    | 7  |    |
| G                         |      |      |     |      |      |     |      |      |     |     | 1   |      |     | 22   |     |     |     |      |     |      |     |    |    |    |    |    |
| H                         |      |      |     |      |      |     |      |      |     | 16  |     |      |     |      |     |     | 1   |      | 1   |      |     |    |    |    |    |    |
| I                         |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| K                         |      |      | 1   |      |      |     |      |      |     |     |     |      |     |      |     | 1   |     |      |     |      |     |    |    |    |    |    |
| L                         |      |      |     |      |      | 1   | 22   | 13   |     |     |     |      |     |      |     |     |     | 22   |     |      |     |    |    |    |    |    |
| M                         |      |      |     |      |      |     |      |      | 1   |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| N                         |      |      |     |      |      |     |      |      |     |     |     |      | 10  |      | 7   | 12  |     |      | 9   |      |     |    |    |    |    |    |
| P                         |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| Q                         | 1    |      |     |      |      | 21  |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| R                         |      |      | 21  |      |      |     |      |      |     |     | 2   |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| S                         | 21   |      |     | 22   | 22   |     | 22   |      |     |     | 19  |      | 1   |      |     |     |     |      |     |      |     |    |    |    |    |    |
| T                         |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     | 8   |     |      |     |      |     |    |    |    |    |    |
| V                         |      |      |     |      |      |     |      |      | 8   |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| W                         |      |      |     |      |      |     |      |      |     | 1   |     |      |     |      |     |     |     |      |     | 22   |     |    |    |    |    |    |
| X                         |      |      |     |      |      |     |      |      |     |     |     |      | 1   |      | 1   |     |     |      | 1   |      |     |    |    |    |    |    |
| Y                         |      |      |     |      |      |     |      |      |     | 4   |     |      | 1   | 11   |     | 21  |     |      |     |      |     |    |    |    | 15 |    |
| -                         |      |      |     |      |      |     |      |      |     |     |     | 22   |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| unknown (?)               |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| not sequenced             |      |      |     |      |      |     |      |      |     |     |     |      |     |      |     |     |     |      |     |      |     |    |    |    |    |    |
| sum of seq <sup>2</sup>   | 22   | 22   | 22  | 22   | 22   | 22  | 22   | 22   | 22  | 22  | 22  | 22   | 22  | 22   | 22  | 22  | 22  | 22   | 22  | 22   | 22  | 22 | 22 | 22 | 22 | 22 |
| oomcaa <sup>3</sup>       | 21   | 22   | 21  | 22   | 22   | 21  | 22   | 22   | 13  | 16  | 19  | 22   | 10  | 22   | 11  | 12  | 21  | 22   | 11  | 22   | 15  |    |    |    |    |    |
| mcaa <sup>4</sup>         | S    | C    | R   | S    | S    | Q   | S    | L    | L   | H   | S   | -    | N   | G    | Y   | N   | Y   | L    | D   | W    | Y   |    |    |    |    |    |
| rel. oomcaa <sup>5</sup>  | 95%  | 100% | 95% | 100% | 100% | 95% | 100% | 100% | 59% | 73% | 86% | 100% | 45% | 100% | 50% | 55% | 95% | 100% | 50% | 100% | 68% |    |    |    |    |    |
| pos occupied <sup>6</sup> | 2    | 1    | 2   | 1    | 1    | 2   | 1    | 1    | 3   | 4   | 3   | 1    | 5   | 1    | 5   | 4   | 2   | 1    | 4   | 1    | 2   |    |    |    |    |    |

Table 4B: Analysis of V kappa subgroup 2

|                           | Framework II |      |     |      |      |      |      |      |     |     |     |      |      | CDR II |     |      |     |      |     |      |      |
|---------------------------|--------------|------|-----|------|------|------|------|------|-----|-----|-----|------|------|--------|-----|------|-----|------|-----|------|------|
| amino acid <sup>1</sup>   | 37           | 38   | 39  | 40   | 41   | 42   | 43   | 44   | 45  | 46  | 47  | 48   | 49   | 50     | 51  | 52   | 53  | 54   | 55  | 56   | 57   |
| A                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      | 14  |      |      |
| B                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| C                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| D                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      | 7   |      |      |
| E                         |              |      |     |      |      |      |      |      | 1   |     |     |      |      |        |     |      |     |      |     |      |      |
| F                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| G                         |              |      |     | 22   |      |      |      |      |     |     |     |      |      | 12     |     |      |     |      | 1   |      | 22   |
| H                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| I                         |              |      |     |      |      |      |      |      |     | 1   | 22  |      |      |        |     |      |     |      |     |      |      |
| K                         |              |      | 15  |      |      |      |      |      |     |     |     |      |      | 5      |     |      |     |      |     |      |      |
| L                         | 16           |      |     |      |      |      |      |      |     | 14  | 21  |      |      | 14     | 1   |      |     |      |     |      |      |
| M                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| N                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      | 18  |      |     |      |      |
| P                         |              |      |     | 22   |      |      |      | 21   |     |     |     |      |      |        |     |      |     |      |     |      |      |
| Q                         | 6            | 22   |     |      |      | 22   |      |      | 12  |     |     |      |      | 1      |     |      |     |      |     |      |      |
| R                         |              |      | 7   |      |      |      |      |      | 8   | 7   |     |      |      | 1      |     |      |     | 22   |     |      |      |
| S                         |              |      |     |      |      | 21   |      |      |     |     |     |      |      |        | 2   | 22   | 2   |      |     | 22   |      |
| T                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      | 1   |      |     |      |      |
| V                         |              |      |     |      |      |      |      |      |     |     | 1   |      |      |        | 6   |      |     |      |     |      |      |
| W                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| X                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| Y                         |              |      |     |      |      |      |      |      |     |     |     |      | 21   |        |     |      | 1   |      |     |      |      |
| -                         |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| unknown (?)               |              |      |     |      |      |      |      |      |     |     |     |      |      |        |     |      |     |      |     |      |      |
| not sequenced             |              |      |     |      |      |      | 1    | 1    | 1   |     |     |      | 1    | 1      | 1   |      |     |      |     |      |      |
| sum of seq <sup>2</sup>   | 22           | 22   | 22  | 22   | 22   | 22   | 21   | 21   | 21  | 22  | 22  | 22   | 21   | 21     | 21  | 22   | 22  | 22   | 22  | 22   | 22   |
| oomcaa <sup>3</sup>       | 16           | 22   | 15  | 22   | 22   | 22   | 21   | 21   | 12  | 14  | 21  | 22   | 21   | 14     | 12  | 22   | 18  | 22   | 14  | 22   | 22   |
| mcaa <sup>4</sup>         | L            | Q    | K   | P    | G    | Q    | S    | P    | Q   | L   | L   | I    | Y    | L      | G   | S    | N   | R    | A   | S    | G    |
| rel. oomcaa <sup>5</sup>  | 73%          | 100% | 68% | 100% | 100% | 100% | 100% | 100% | 57% | 64% | 95% | 100% | 100% | 67%    | 57% | 100% | 82% | 100% | 64% | 100% | 100% |
| pos occupied <sup>6</sup> | 2            | 1    | 2   | 1    | 1    | 1    | 1    | 1    | 3   | 3   | 2   | 1    | 1    | 4      | 4   | 1    | 4   | 1    | 3   | 1    | 1    |

Table 4B: Analysis of V kappa subgroup 2

4B: Analysis of V kappa subgroup 2

|                            | Framework III |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
|----------------------------|---------------|------|------|-----|-----|------|-----|-----|------|------|-----|------|------|------|-----|------|-----|------|-----|-----|------|--|
| amino acid <sup>1</sup>    | 58            | 59   | 60   | 61  | 62  | 63   | 64  | 65  | 66   | 67   | 68  | 69   | 70   | 71   | 72  | 73   | 74  | 75   | 76  | 77  | 78   |  |
| A                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| B                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| C                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| D                          |               |      | 22   |     |     |      | 1   |     |      |      | 1   |      | 22   |      |     |      |     |      |     |     |      |  |
| E                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| F                          |               |      |      |     | 21  |      |     |     |      |      |     |      |      | 22   |     |      |     |      |     |     |      |  |
| G                          |               |      |      |     |     |      | 21  |     | 22   |      | 21  |      |      |      |     |      |     |      |     |     |      |  |
| H                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| I                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      | 1   | 21   |     |     |      |  |
| K                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      | 19  |      |     |     |      |  |
| L                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     | 21   | 1   |      |     |     |      |  |
| M                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| N                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| P                          |               | 22   |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| Q                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| R                          |               |      |      | 20  |     |      |     | 1   |      |      |     |      |      |      |     |      |     |      |     | 20  |      |  |
| S                          |               |      |      | 1   |     | 22   |     | 21  |      | 22   |     |      |      |      |     |      |     |      | 20  | 1   |      |  |
| T                          |               |      |      | 1   |     |      |     |     |      |      |     | 22   |      |      | 21  |      |     |      | 1   |     |      |  |
| V                          | 22            |      |      |     | 1   |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     | 21   |  |
| W                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| X                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| Y                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| -                          |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      |     |      |     |     |      |  |
| unknown (?)                |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     | 1    |     |      |     |     |      |  |
| not sequenced <sup>2</sup> |               |      |      |     |     |      |     |     |      |      |     |      |      |      |     |      | 1   | 1    | 1   | 1   | 1    |  |
| sum of seq <sup>3</sup>    | 22            | 22   | 22   | 22  | 22  | 22   | 22  | 22  | 22   | 22   | 22  | 22   | 22   | 22   | 22  | 21   | 21  | 21   | 21  | 21  | 21   |  |
| oomcaa <sup>4</sup>        | 22            | 22   | 22   | 20  | 21  | 22   | 21  | 21  | 22   | 22   | 21  | 22   | 22   | 22   | 21  | 21   | 19  | 21   | 20  | 20  | 21   |  |
| mcaa <sup>5</sup>          | V             | P    | D    | R   | F   | S    | G   | S   | G    | S    | G   | T    | D    | F    | T   | L    | K   | I    | S   | R   | V    |  |
| rel. oomcaa <sup>6</sup>   | 100%          | 100% | 100% | 91% | 95% | 100% | 95% | 95% | 100% | 100% | 95% | 100% | 100% | 100% | 95% | 100% | 90% | 100% | 95% | 95% | 100% |  |
| pos occupied <sup>7</sup>  | 1             | 1    | 1    | 3   | 2   | 1    | 2   | 2   | 1    | 1    | 2   | 1    | 1    | 1    | 1   | 1    | 3   | 1    | 2   | 2   | 1    |  |

Table 4B: Analysis of V kappa subgroup 2

|                           |     |     |     |      |      |      |     |      |      |      | CDR III |     |     |     |     |     |     |     |      |      |      |  |
|---------------------------|-----|-----|-----|------|------|------|-----|------|------|------|---------|-----|-----|-----|-----|-----|-----|-----|------|------|------|--|
| amino acid <sup>1</sup>   | 79  | 80  | 81  | 82   | 83   | 84   | 85  | 86   | 87   | 88   | 89      | 90  | 91  | 92  | 93  | 94  | 95  | A   | B    | C    | D    |  |
| A                         |     | 20  |     |      |      |      |     |      |      |      |         |     | 14  |     |     | 1   |     |     |      |      |      |  |
| B                         |     |     |     |      |      |      |     |      |      |      |         | 1   |     |     | 1   |     |     |     |      |      |      |  |
| C                         |     |     |     |      |      |      |     |      |      | 21   |         |     |     |     |     |     |     |     |      |      |      |  |
| D                         |     |     | 1   | 21   |      |      |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| E                         | 19  | 20  |     |      |      |      |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| F                         |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| G                         | 1   |     |     |      |      | 21   |     |      |      |      |         |     | 6   |     |     | 1   |     | 2   |      |      |      |  |
| H                         |     |     |     |      |      |      |     |      |      |      |         |     | 1   |     | 7   |     |     |     |      |      |      |  |
| I                         |     |     |     |      |      |      | 1   |      |      |      |         |     |     |     |     | 1   |     |     |      |      |      |  |
| K                         |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| L                         |     |     |     |      |      |      | 1   |      |      |      |         |     |     | 12  |     |     | 2   |     |      |      |      |  |
| M                         |     |     |     |      |      |      |     |      |      | 21   |         |     |     |     |     |     |     |     |      |      |      |  |
| N                         |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| P                         |     | 1   |     |      |      |      |     |      |      |      |         |     |     |     |     | 2   | 16  | 1   |      |      |      |  |
| Q                         | 1   |     |     |      |      |      |     |      |      |      | 20      |     |     | 13  |     |     |     |     |      |      |      |  |
| R                         |     |     |     |      |      |      |     |      |      |      |         |     |     | 1   |     |     |     |     |      |      |      |  |
| S                         |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     | 3   | 2   |     |      |      |      |  |
| T                         |     |     |     |      |      |      |     |      |      |      |         |     |     | 8   |     | 7   |     |     |      |      |      |  |
| V                         |     |     |     | 21   |      | 19   |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| W                         |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     | 6   |     |     |      |      |      |  |
| X                         |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| Y                         |     |     |     |      |      |      |     | 21   | 21   |      |         |     |     |     |     |     |     |     |      |      |      |  |
| -                         |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     |     |     | 14  | 17   | 17   | 17   |  |
| unknown (?)               |     |     |     |      |      |      |     |      |      |      |         |     |     |     |     |     |     |     |      |      |      |  |
| not sequenced             | 1   | 1   | 1   | 1    | 1    | 1    | 1   | 1    | 1    | 1    | 1       | 1   | 1   | 1   | 1   | 1   | 2   | 5   | 5    | 5    | 5    |  |
| sum of seq <sup>2</sup>   | 21  | 21  | 21  | 21   | 21   | 21   | 21  | 21   | 21   | 21   | 21      | 21  | 21  | 21  | 21  | 21  | 20  | 17  | 17   | 17   | 17   |  |
| oomcaa <sup>3</sup>       | 19  | 20  | 20  | 21   | 21   | 21   | 19  | 21   | 21   | 21   | 21      | 20  | 14  | 12  | 13  | 7   | 16  | 14  | 17   | 17   | 17   |  |
| mcaa <sup>4</sup>         | E   | A   | E   | D    | V    | G    | V   | Y    | Y    | C    | M       | Q   | A   | L   | Q   | T   | P   | -   | -    | -    | -    |  |
| rel. oomcaa <sup>5</sup>  | 90% | 95% | 95% | 100% | 100% | 100% | 90% | 100% | 100% | 100% | 100%    | 95% | 67% | 57% | 62% | 33% | 80% | 82% | 100% | 100% | 100% |  |
| pos occupied <sup>6</sup> | 3   | 2   | 2   | 1    | 1    | 1    | 3   | 1    | 1    | 1    | 1       | 2   | 3   | 3   | 3   | 7   | 3   | 3   | 1    | 1    | 1    |  |

Table 4B: Analysis of V kappa subgroup 2

| amino acid <sup>1</sup>   | Framework IV |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | sum |
|---------------------------|--------------|------|-----|------|------|------|-----|------|------|-----|-----|-----|------|------|------|------|----|--|-----|
|                           | E            | F    | 96  | 97   | 98   | 99   | 100 | 101  | 102  | 103 | 104 | 105 | 106  | A    | 107  | 108  |    |  |     |
| A                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 71  |
| B                         |              |      |     |      |      |      |     |      |      |     |     | 1   |      |      |      |      |    |  | 3   |
| C                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 43  |
| D                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 112 |
| E                         |              |      |     |      |      |      |     |      |      |     |     | 13  |      |      |      |      |    |  | 71  |
| F                         |              |      | 1   |      | 17   |      |     |      |      |     |     |     |      |      |      |      |    |  | 72  |
| G                         |              |      |     |      |      | 17   | 2   | 16   |      |     |     | 1   |      |      |      |      |    |  | 233 |
| H                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 26  |
| I                         |              |      | 3   |      |      |      |     |      |      |     |     |     |      | 14   |      |      |    |  | 94  |
| K                         |              |      |     |      |      |      |     |      |      | 12  |     |     |      |      |      | 13   |    |  | 66  |
| L                         |              |      | 2   |      |      |      |     |      |      |     | 11  |     |      |      |      |      |    |  | 219 |
| M                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 37  |
| N                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 56  |
| P                         |              |      | 1   |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 159 |
| Q                         |              |      | 1   |      |      |      | 14  |      |      |     |     |     |      |      |      |      |    |  | 159 |
| R                         |              |      |     |      |      |      |     |      |      | 4   |     |     |      |      |      |      | 12 |  | 126 |
| S                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 325 |
| T                         |              |      |     | 17   |      |      |     |      | 16   |     |     |     |      |      |      |      |    |  | 140 |
| V                         |              |      |     |      |      |      |     |      |      |     |     | 5   |      |      |      |      |    |  | 146 |
| W                         |              |      | 2   |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 31  |
| X                         |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 3   |
| Y                         |              |      | 7   |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 123 |
| -                         | 17           | 17   |     |      |      |      |     |      |      |     |     |     |      | 13   |      |      |    |  | 134 |
| unknown (?)               |              |      |     |      |      |      |     |      |      |     |     |     |      |      |      |      |    |  | 2   |
| not sequenced             | 5            | 5    | 5   | 5    | 5    | 5    | 6   | 6    | 6    | 6   | 6   | 7   | 8    | 9    | 9    | 10   |    |  | 211 |
| sum of seq <sup>2</sup>   | 17           | 17   | 17  | 17   | 17   | 17   | 16  | 16   | 16   | 16  | 16  | 15  | 14   | 13   | 13   | 12   |    |  |     |
| oomcaa <sup>3</sup>       | 17           | 17   | 7   | 17   | 17   | 17   | 14  | 16   | 16   | 12  | 11  | 13  | 14   | 13   | 13   | 12   |    |  |     |
| mcaa <sup>4</sup>         | -            | -    | Y   | T    | F    | G    | Q   | G    | T    | K   | L   | E   | I    | -    | K    | R    |    |  |     |
| rel. oomcaa <sup>5</sup>  | 100%         | 100% | 41% | 100% | 100% | 100% | 88% | 100% | 100% | 75% | 69% | 87% | 100% | 100% | 100% | 100% |    |  |     |
| pos occupied <sup>6</sup> | 1            | 1    | 7   | 1    | 1    | 1    | 2   | 1    | 1    | 2   | 2   | 3   | 1    | 1    | 1    | 1    |    |  |     |

Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | Framework I |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
|---------------------------|-------------|-----|-----|-----|-----|------|-----|------|-----|-----|-----|-----|-----|-----|-----|------|
|                           | 1           | 2   | 3   | 4   | 5   | 6    | 7   | 8    | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16   |
| A                         |             | 5   |     |     |     |      | 2   |      | 27  |     |     |     |     |     | 1   |      |
| B                         | 1           |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| C                         |             |     |     |     |     |      |     |      |     |     |     | 2   |     |     |     |      |
| D                         | 2           |     |     |     |     |      |     |      | 14  |     |     |     |     |     |     |      |
| E                         | 76          |     | 27  |     |     |      |     |      |     |     |     |     |     |     |     |      |
| F                         |             | 1   |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| G                         | 1           |     |     |     |     |      |     |      | 82  |     |     |     |     |     | 1   | 152  |
| H                         |             |     |     |     |     |      |     |      |     | 1   |     |     |     |     |     |      |
| I                         |             | 75  |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| K                         | 3           |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| L                         |             | 4   | 1   | 104 |     |      | 1   |      |     |     | 150 | 129 |     |     | 1   |      |
| M                         | 5           |     |     | 13  |     |      |     |      |     |     |     |     |     |     |     |      |
| N                         |             |     |     |     |     |      |     |      |     |     |     |     |     | 5   |     |      |
| P                         |             |     |     |     |     |      |     | 124  |     |     |     |     |     |     | 147 |      |
| Q                         |             |     |     |     |     | 123  |     |      |     |     |     |     |     |     |     |      |
| R                         |             |     |     |     | 1   |      |     |      |     |     |     |     |     |     |     |      |
| S                         |             |     |     |     |     |      | 119 |      | 3   | 1   |     | 150 | 1   | 141 |     |      |
| T                         |             | 2   |     |     | 117 |      |     |      |     | 147 |     |     |     | 5   | 1   |      |
| V                         |             | 1   | 89  | 1   |     |      | 1   |      |     |     | 1   |     | 22  |     | 1   |      |
| W                         |             |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| X                         |             |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| Y                         |             |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| -                         |             |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| unknown (?)               |             |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| not sequenced             |             |     |     |     |     |      |     |      |     |     |     |     |     |     |     |      |
| sum of seq <sup>2</sup>   | 88          | 88  | 117 | 118 | 118 | 123  | 123 | 124  | 126 | 149 | 151 | 152 | 152 | 152 | 152 | 152  |
| oomcaa <sup>3</sup>       | 76          | 75  | 89  | 104 | 117 | 123  | 119 | 124  | 82  | 147 | 150 | 150 | 129 | 141 | 147 | 152  |
| mcaa <sup>4</sup>         | E           | I   | V   | L   | T   | Q    | S   | P    | G   | T   | L   | S   | L   | S   | P   | G    |
| rel. oomcaa <sup>5</sup>  | 86%         | 85% | 76% | 88% | 99% | 100% | 97% | 100% | 65% | 99% | 99% | 99% | 85% | 93% | 97% | 100% |
| pos occupied <sup>6</sup> | 6           | 6   | 3   | 3   | 2   | 1    | 4   | 1    | 4   | 3   | 2   | 2   | 3   | 4   | 6   | 1    |



Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | CDRI |     |     |     |     |     |      |     |     |     |     |     |      |      |      |      |
|---------------------------|------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|------|------|------|------|
|                           | 17   | 18  | 19  | 20  | 21  | 22  | 23   | 24  | 25  | 26  | 27  | A   | B    | C    | D    | E    |
| A                         |      |     | 178 | 2   |     |     |      |     | 166 | 1   |     |     |      |      |      |      |
| B                         |      |     |     |     |     |     |      |     |     |     |     |     |      |      |      |      |
| C                         |      |     |     |     |     |     | 181  |     |     | 1   |     |     |      |      |      |      |
| D                         | 6    |     |     |     |     |     |      |     |     |     |     |     |      |      |      |      |
| E                         | 146  | 1   |     |     |     |     |      |     |     |     | 1   |     |      |      |      |      |
| F                         |      |     |     |     | 7   | 1   |      |     |     |     |     |     |      |      |      |      |
| G                         | 1    | 1   |     |     |     |     |      |     | 1   | 1   |     | 1   |      |      |      |      |
| H                         |      |     |     |     |     |     |      |     |     |     | 17  |     |      |      |      |      |
| I                         |      | 1   |     | 5   | 2   |     |      |     |     |     |     |     |      |      |      |      |
| K                         |      | 1   |     |     |     |     |      | 5   |     |     |     |     |      |      |      |      |
| L                         |      |     |     | 173 |     |     |      |     |     |     | 1   | 1   |      |      |      |      |
| M                         |      |     |     |     |     |     |      |     |     |     |     |     |      |      |      |      |
| N                         |      |     |     |     |     |     |      |     |     |     |     | 9   |      |      |      |      |
| P                         |      |     |     |     |     |     |      |     |     |     |     |     |      |      |      |      |
| Q                         |      |     |     |     |     |     |      |     |     |     | 159 |     |      |      |      |      |
| R                         |      | 175 |     |     |     |     |      | 176 |     | 1   | 1   | 10  |      |      |      |      |
| S                         |      |     |     |     |     | 180 |      |     | 7   | 175 |     | 87  |      |      |      |      |
| T                         |      | 1   |     | 174 |     |     |      |     | 7   | 2   |     | 1   |      |      |      |      |
| V                         |      | 1   | 4   | 1   |     |     |      |     |     | 1   |     | 1   |      |      |      |      |
| W                         |      |     |     |     |     |     |      | 1   |     |     |     |     |      |      |      |      |
| X                         |      |     |     |     |     |     |      |     |     |     |     |     |      |      |      |      |
| Y                         |      |     |     |     |     | 1   |      |     |     |     | 1   |     |      |      |      |      |
| -                         |      |     |     |     |     |     |      |     |     |     |     | 72  | 182  | 182  | 182  | 182  |
| unknown (?)               |      |     |     |     |     |     |      |     |     |     | 1   |     |      |      |      |      |
| not sequenced             |      |     |     |     |     |     |      |     |     |     |     |     |      |      |      |      |
| sum of seq <sup>2</sup>   | 153  | 181 | 182 | 182 | 182 | 182 | 181  | 182 | 182 | 181 | 181 | 182 | 182  | 182  | 182  | 182  |
| oomcaa <sup>1</sup>       | 146  | 175 | 178 | 174 | 173 | 180 | 181  | 176 | 166 | 175 | 159 | 87  | 182  | 182  | 182  | 182  |
| mcaa <sup>4</sup>         | E    | R   | A   | T   | L   | S   | C    | R   | A   | S   | Q   | S   | -    | -    | -    | -    |
| rel. oomcaa <sup>5</sup>  | 95%  | 97% | 98% | 96% | 95% | 99% | 100% | 97% | 91% | 97% | 88% | 48% | 100% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 3    | 7   | 2   | 4   | 3   | 3   | 1    | 3   | 5   | 6   | 6   | 8   | 1    | 1    | 1    | 1    |

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Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   |      |     |     |     |     |     |     |     |      |     |     |     |     |     |      | Framewo |  |  |  |  |  |  |
|---------------------------|------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|------|---------|--|--|--|--|--|--|
|                           | F    | 28  | 29  | 30  | 31  | 32  | 33  | 34  | 35   | 36  | 37  | 38  | 39  | 40  | 41   | 42      |  |  |  |  |  |  |
| A                         |      |     |     | 1   | 1   |     |     | 181 |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| B                         |      |     |     |     |     |     |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| C                         |      |     |     |     |     |     |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| D                         |      |     | 1   | 1   | 2   | 1   |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| E                         |      |     |     |     |     | 1   |     |     |      |     |     |     | 1   |     |      | 1       |  |  |  |  |  |  |
| F                         |      | 1   |     |     |     | 7   |     |     |      | 1   |     |     |     |     |      |         |  |  |  |  |  |  |
| G                         |      |     | 2   | 7   | 3   | 1   |     | 2   |      |     |     |     |     | 1   | 184  |         |  |  |  |  |  |  |
| H                         |      |     | 1   |     |     | 2   |     |     |      | 1   |     | 12  | 1   | 1   |      |         |  |  |  |  |  |  |
| I                         |      | 24  | 4   | 1   | 1   |     |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| K                         |      |     |     | 1   | 1   |     |     |     |      |     |     |     | 153 |     |      |         |  |  |  |  |  |  |
| L                         |      | 8   | 1   |     |     | 1   | 176 |     |      |     |     | 3   |     |     |      | 2       |  |  |  |  |  |  |
| M                         |      |     |     |     |     |     |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| N                         |      |     | 3   | 12  | 25  | 32  |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| P                         |      |     |     |     | 1   |     |     |     |      |     |     |     |     | 170 |      |         |  |  |  |  |  |  |
| Q                         |      |     |     |     | 1   | 1   |     |     |      | 183 | 167 | 1   |     |     |      | 181     |  |  |  |  |  |  |
| R                         |      |     | 10  | 3   | 18  | 16  |     | 1   |      |     | 1   |     | 27  | 5   |      |         |  |  |  |  |  |  |
| S                         |      | 72  | 86  | 151 | 118 | 4   |     |     |      |     |     |     |     | 5   |      |         |  |  |  |  |  |  |
| T                         |      | 1   | 1   | 3   | 8   | 1   |     |     |      |     |     |     | 1   |     |      |         |  |  |  |  |  |  |
| V                         |      | 76  | 68  |     | 1   |     | 7   |     |      |     |     | 3   |     | 2   |      |         |  |  |  |  |  |  |
| W                         |      |     | 5   |     |     |     |     |     | 185  |     |     |     |     |     |      |         |  |  |  |  |  |  |
| X                         |      |     |     |     |     |     |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| Y                         |      |     |     | 1   | 1   | 115 |     |     |      | 183 |     |     |     |     |      |         |  |  |  |  |  |  |
| -                         | 182  |     |     |     |     |     |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| unknown (?)               |      |     |     |     |     |     |     |     |      |     | 1   |     |     |     |      |         |  |  |  |  |  |  |
| not sequenced             |      |     |     |     |     |     |     |     |      |     |     |     |     |     |      |         |  |  |  |  |  |  |
| sum of seq <sup>2</sup>   | 182  | 182 | 182 | 181 | 181 | 182 | 183 | 184 | 185  | 185 | 185 | 185 | 184 | 184 | 184  | 184     |  |  |  |  |  |  |
| oomcaa <sup>1</sup>       | 182  | 76  | 86  | 151 | 118 | 115 | 176 | 181 | 185  | 183 | 183 | 167 | 153 | 170 | 184  | 181     |  |  |  |  |  |  |
| mcaa <sup>1</sup>         | -    | V   | S   | S   | S   | Y   | L   | A   | W    | Y   | Q   | Q   | K   | P   | G    | Q       |  |  |  |  |  |  |
| rel. oomcaa <sup>3</sup>  | 100% | 42% | 47% | 83% | 65% | 63% | 96% | 98% | 100% | 99% | 99% | 90% | 83% | 92% | 100% | 98%     |  |  |  |  |  |  |
| pos occupied <sup>4</sup> | 1    | 6   | 11  | 10  | 13  | 12  | 2   | 3   | 1    | 3   | 2   | 4   | 6   | 6   | 1    | 3       |  |  |  |  |  |  |

Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | CDR II |     |     |     |     |     |     |     |     | CDR II |     |     |     |     |     |     |  |  |
|---------------------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|--------|-----|-----|-----|-----|-----|-----|--|--|
|                           | 43     | 44  | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52     | 53  | 54  | 55  | 56  | 57  | 58  |  |  |
| A                         | 176    |     |     |     |     |     |     | 4   | 147 |        |     |     | 176 | 1   |     |     |  |  |
| B                         |        |     |     |     |     |     |     |     |     |        |     |     |     |     |     |     |  |  |
| C                         |        |     |     |     |     |     |     |     | 1   |        |     |     |     |     |     |     |  |  |
| D                         |        |     |     |     |     |     |     | 43  |     |        |     |     | 2   |     | 4   |     |  |  |
| E                         |        |     |     |     |     |     |     |     |     |        |     |     |     |     |     |     |  |  |
| F                         |        |     |     | 1   |     | 1   | 4   |     |     |        |     |     |     |     |     |     |  |  |
| G                         |        |     |     |     |     |     |     | 125 |     |        |     |     | 2   | 10  | 179 |     |  |  |
| H                         |        |     |     |     |     |     | 9   |     | 1   |        |     |     |     |     |     |     |  |  |
| I                         |        |     |     |     |     | 178 |     |     |     |        |     |     |     |     | 1   | 168 |  |  |
| K                         |        |     | 1   |     |     |     |     |     |     |        | 7   | 1   |     |     |     |     |  |  |
| L                         |        | 1   |     | 179 | 174 | 1   |     |     |     |        |     |     |     |     |     |     |  |  |
| M                         |        |     |     |     |     | 3   |     |     |     |        | 1   |     |     |     |     |     |  |  |
| N                         |        |     | 1   |     |     |     |     | 1   |     | 53     |     |     |     | 2   |     |     |  |  |
| P                         | 5      | 184 |     |     |     |     |     |     |     | 2      |     |     | 2   | 2   |     |     |  |  |
| Q                         |        |     |     |     |     |     | 1   |     |     |        |     |     |     |     |     |     |  |  |
| R                         |        |     | 182 |     |     |     |     | 1   |     | 4      | 180 |     |     |     |     |     |  |  |
| S                         |        |     |     |     |     |     | 3   | 6   | 4   | 179    | 74  | 1   |     | 5   |     |     |  |  |
| T                         | 3      |     |     |     |     |     |     |     | 11  | 2      | 44  |     |     | 164 |     | 2   |  |  |
| V                         |        |     |     | 3   | 9   |     |     | 3   | 19  |        |     |     | 3   |     |     | 15  |  |  |
| W                         |        |     |     |     |     |     | 1   |     |     |        |     | 1   |     |     |     |     |  |  |
| X                         |        |     |     |     |     |     |     |     |     |        |     |     |     |     |     |     |  |  |
| Y                         |        |     |     |     |     |     | 165 |     |     |        |     |     |     |     |     | 2   |  |  |
| -                         |        |     |     |     |     |     |     |     |     |        |     |     |     |     |     |     |  |  |
| unknown (?)               |        |     | 1   |     |     |     |     |     |     |        |     |     |     |     |     |     |  |  |
| not sequenced             |        |     |     |     |     |     |     |     |     |        |     |     |     |     |     |     |  |  |
| sum of seq <sup>2</sup>   | 184    | 185 | 185 | 183 | 183 | 183 | 183 | 183 | 183 | 183    | 183 | 183 | 185 | 185 | 185 | 185 |  |  |
| oomcaa <sup>3</sup>       | 176    | 184 | 182 | 179 | 174 | 178 | 165 | 125 | 147 | 179    | 74  | 180 | 176 | 164 | 179 | 168 |  |  |
| mcaa <sup>4</sup>         | A      | P   | R   | L   | L   | I   | Y   | G   | A   | S      | S   | R   | A   | T   | G   | I   |  |  |
| rel. oomcaa <sup>5</sup>  | 96%    | 99% | 98% | 98% | 95% | 97% | 90% | 68% | 80% | 98%    | 40% | 98% | 95% | 89% | 97% | 91% |  |  |
| pos occupied <sup>6</sup> | 3      | 2   | 3   | 3   | 2   | 4   | 6   | 7   | 6   | 3      | 6   | 4   | 5   | 7   | 3   | 3   |  |  |

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Table 4C: Analysis of V kappa subgroup 3

|                           | Framework III |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 59            | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67   | 68  | 69  | 70  | 71  | 72  | 73  | 74  |
| A                         |               | 68  |     |     |     |     |     | 3   |      | 5   | 3   | 1   |     | 3   |     |     |
| B                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| C                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| D                         |               | 112 |     |     |     | 1   |     |     |      |     |     | 152 |     |     |     |     |
| E                         |               |     |     |     |     |     |     | 1   |      | 1   |     | 30  |     |     |     |     |
| F                         |               |     |     | 183 |     |     |     |     |      |     |     |     | 183 |     | 2   |     |
| G                         |               |     |     |     |     | 184 | 3   | 178 | —    | 177 |     |     |     |     |     |     |
| H                         |               | 1   |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| I                         |               |     |     | 1   |     |     |     |     |      |     |     |     |     | 1   |     | 3   |
| K                         |               |     | 1   |     |     |     |     |     |      |     |     |     |     |     |     |     |
| L                         |               |     |     | 1   |     |     |     |     |      |     |     |     |     |     | 182 |     |
| M                         |               |     |     |     |     |     |     | 1   |      |     |     |     |     |     |     |     |
| N                         |               | 1   |     |     |     |     |     |     |      |     |     |     |     | 1   |     |     |
| P                         | 177           |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Q                         |               |     |     |     |     |     |     |     |      |     |     | 1   |     |     |     |     |
| R                         |               |     | 182 |     | 2   |     | 1   |     |      |     | 2   |     |     |     |     |     |
| S                         | 7             |     |     |     | 180 |     | 179 |     | 185  |     | 3   |     |     | 7   |     | 2   |
| T                         | 1             |     | 2   |     | 3   |     | 2   |     |      |     | 177 |     |     | 172 |     | 179 |
| V                         |               | 3   |     |     |     |     |     | 1   |      | 1   |     |     |     |     |     |     |
| W                         |               |     |     |     |     |     |     |     |      | 1   |     |     |     |     |     |     |
| X                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Y                         |               |     |     |     |     |     |     |     |      |     |     |     | 1   |     |     |     |
| -                         |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| unknown (?)               |               |     |     |     |     |     |     | 1   |      |     |     |     |     |     |     |     |
| not sequenced             |               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 185           | 185 | 185 | 185 | 185 | 185 | 185 | 185 | 185  | 185 | 185 | 184 | 184 | 184 | 184 | 184 |
| oomcaa <sup>3</sup>       | 177           | 112 | 182 | 183 | 180 | 184 | 179 | 178 | 185  | 177 | 177 | 152 | 183 | 172 | 182 | 179 |
| mcaa <sup>4</sup>         | P             | D   | R   | F   | S   | G   | S   | G   | S    | G   | T   | D   | F   | T   | L   | T   |
| rel. oomcaa <sup>5</sup>  | 96%           | 61% | 98% | 99% | 97% | 99% | 97% | 96% | 100% | 96% | 96% | 83% | 99% | 93% | 99% | 97% |
| pos occupied <sup>6</sup> | 3             | 5   | 3   | 3   | 3   | 2   | 4   | 5   | 1    | 5   | 4   | 4   | 2   | 5   | 2   | 3   |

Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | 75  | 76  | 77  | 78  | 79  | 80  | 81  | 82  | 83  | 84  | 85  | 86  | 87  | 88  | 89  | 90      |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---------|
| A                         |     |     |     |     |     |     | 3   |     |     | 174 |     |     |     |     |     |         |
| B                         |     |     |     |     | 1   |     |     |     |     |     |     |     |     |     |     |         |
| C                         |     |     |     |     |     |     |     |     | 2   |     |     |     | 1   | 182 |     |         |
| D                         |     |     | 1   |     |     |     | 3   | 182 |     |     |     |     |     |     |     |         |
| E                         |     |     |     |     | 149 |     | 175 |     |     |     |     |     |     |     |     | 2       |
| F                         |     | 1   |     |     |     |     |     |     | 178 |     | 2   | 1   | 4   |     |     |         |
| G                         |     |     | 3   |     |     |     |     | 1   |     | 2   |     |     |     |     |     |         |
| H                         |     |     |     |     |     |     |     |     |     |     | 1   |     |     |     | 1   | 7       |
| I                         | 178 |     |     |     |     |     |     | 1   | 1   |     | 9   |     |     |     |     |         |
| K                         |     |     |     |     |     |     | 1   |     |     |     |     |     |     |     |     |         |
| L                         |     |     |     | 178 |     | 1   |     |     | 1   |     | 7   |     | 1   |     |     | 1       |
| M                         |     |     |     |     |     |     |     |     |     | 1   | 5   |     |     |     |     |         |
| N                         | 1   | 5   |     |     |     |     |     |     |     |     |     |     |     |     |     |         |
| P                         |     |     |     |     |     | 149 |     |     |     |     |     |     |     |     |     |         |
| Q                         |     |     |     |     | 34  |     |     |     |     |     |     |     |     |     | 1   | 181 155 |
| R                         |     | 1   | 111 |     |     |     |     |     |     | 3   |     |     |     |     |     | 1       |
| S                         |     | 169 | 65  |     |     | 34  |     |     | 1   |     |     |     | 2   |     |     |         |
| T                         |     | 8   | 4   |     |     |     |     |     |     | 1   |     |     |     |     |     | 8       |
| V                         | 4   |     |     | 6   |     |     |     |     | 1   | 3   | 159 |     |     |     |     | 7       |
| W                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |         |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |         |
| Y                         | 1   |     |     |     |     |     |     |     |     |     | 1   | 183 | 176 |     | 1   | 2       |
| -                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |         |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |         |
| not sequenced             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |         |
| sum of seq <sup>2</sup>   | 184 | 184 | 184 | 184 | 184 | 184 | 182 | 184 | 184 | 184 | 184 | 184 | 184 | 183 | 183 | 183     |
| oomcaa <sup>3</sup>       | 178 | 169 | 111 | 178 | 149 | 149 | 175 | 182 | 178 | 174 | 159 | 183 | 176 | 182 | 181 | 155     |
| mcaa <sup>4</sup>         | I   | S   | R   | L   | E   | P   | E   | D   | F   | A   | V   | Y   | Y   | C   | Q   | Q       |
| rel. oomcaa <sup>5</sup>  | 97% | 92% | 60% | 97% | 81% | 81% | 96% | 99% | 97% | 95% | 86% | 99% | 96% | 99% | 99% | 85%     |
| pos occupied <sup>6</sup> | 4   | 5   | 5   | 2   | 3   | 3   | 4   | 3   | 6   | 6   | 7   | 2   | 5   | 2   | 3   | 8       |

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Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |      |      |      |      |     |     |     | 100 |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|------|------|------|------|-----|-----|-----|-----|
|                           | 91      | 92  | 93  | 94  | 95  | A   | B   | C    | D    | E    | F    | 96  | 97  | 98  |     |
| A                         |         | 1   | 8   | 3   | 3   |     |     |      |      |      |      |     |     |     | 1   |
| B                         |         |     |     |     |     |     |     |      |      |      |      |     |     |     |     |
| C                         | 2       |     |     | 1   |     |     |     |      |      |      |      | 2   |     |     |     |
| D                         |         | 8   | 5   |     |     |     |     |      |      |      |      |     | 1   |     |     |
| E                         |         | 2   |     |     |     |     |     |      |      |      |      | 1   |     |     |     |
| F                         | 5       |     | 2   |     |     |     |     |      |      |      |      | 7   | 166 |     |     |
| G                         | 1       | 104 | 15  |     | 1   | 1   | 2   |      |      |      |      | 1   |     | 166 | 41  |
| H                         | 4       | 1   |     |     |     |     |     |      |      |      |      | 2   |     |     |     |
| I                         |         |     | 1   |     |     | 1   |     |      |      |      |      | 4   |     |     |     |
| K                         |         |     | 2   |     |     | 1   |     |      |      |      |      | 1   |     |     | 1   |
| L                         |         |     |     | 2   | 7   | 5   |     |      |      |      |      | 42  |     |     |     |
| M                         |         | 1   |     |     | 1   | 2   |     |      |      |      |      |     |     |     |     |
| N                         |         | 28  | 71  |     |     |     |     |      |      |      |      | 1   |     |     |     |
| P                         |         |     |     | 1   | 139 | 24  |     |      |      |      |      | 7   | 2   |     | 9   |
| Q                         | 1       |     | 1   |     | 3   | 1   |     |      |      |      |      | 3   |     |     | 114 |
| R                         | 34      | 2   | 3   |     | 2   | 2   |     |      |      |      |      | 19  |     |     |     |
| S                         | 2       | 33  | 58  | 102 | 15  | 2   |     |      |      |      |      | 1   | 8   |     |     |
| T                         |         | 2   | 13  | 1   | 1   | 2   |     |      |      |      |      | 1   | 154 |     |     |
| V                         |         |     |     |     | 3   | 1   |     |      |      |      |      | 2   |     |     |     |
| W                         |         |     |     | 69  |     |     |     |      |      |      |      | 24  |     |     |     |
| X                         |         |     |     |     |     |     |     |      |      |      |      |     |     |     |     |
| Y                         | 134     | 1   | 1   |     |     |     |     |      |      |      |      | 43  |     |     |     |
| -                         |         |     | 3   | 3   | 7   | 127 | 167 | 169  | 169  | 169  | 169  | 8   | 1   | 1   | 1   |
| unknown (?)               |         |     |     |     |     |     |     |      |      |      |      |     |     |     |     |
| not sequenced             |         |     |     |     |     | 14  | 14  | 14   | 14   | 14   | 14   | 14  | 17  | 16  | 16  |
| sum of seq <sup>2</sup>   | 183     | 183 | 183 | 182 | 182 | 169 | 169 | 169  | 169  | 169  | 169  | 169 | 166 | 167 | 167 |
| oomcaa <sup>1</sup>       | 134     | 104 | 71  | 102 | 139 | 127 | 167 | 169  | 169  | 169  | 169  | 43  | 154 | 166 | 114 |
| mcaa <sup>1</sup>         | Y       | G   | N   | S   | P   | -   | -   | -    | -    | -    | -    | Y   | T   | F   | Q   |
| rel. oomcaa <sup>3</sup>  | 73%     | 57% | 39% | 56% | 76% | 75% | 99% | 100% | 100% | 100% | 100% | 25% | 93% | 99% | 68% |
| pos occupied <sup>4</sup> | 8       | 11  | 13  | 8   | 11  | 12  | 2   | 1    | 1    | 1    | 1    | 18  | 5   | 2   | 6   |

Table 4C: Analysis of V kappa subgroup 3

| amino acid <sup>1</sup>    | Framework IV |     |     |     |     |     |      |     |     | sum  |
|----------------------------|--------------|-----|-----|-----|-----|-----|------|-----|-----|------|
|                            | 101          | 102 | 103 | 104 | 105 | 106 | A    | 107 | 108 |      |
| A                          |              |     |     |     |     |     |      |     |     | 1345 |
| B                          |              |     |     |     |     |     |      |     |     | 2    |
| C                          |              |     |     |     |     |     |      |     |     | 375  |
| D                          |              |     |     |     | 23  |     |      |     |     | 564  |
| E                          |              |     | 3   |     | 141 |     |      |     |     | 759  |
| F                          |              |     |     |     |     | 6   |      |     |     | 765  |
| G                          | 166          |     |     |     |     |     |      |     | 1   | 1804 |
| H                          |              |     |     |     | 1   |     |      |     |     | 64   |
| I                          |              |     |     |     |     | 143 |      |     |     | 803  |
| K                          |              |     | 152 |     |     |     |      | 157 |     | 489  |
| L                          |              |     |     | 54  |     | 1   |      |     | 2   | 1596 |
| M                          |              |     |     |     |     | 3   |      |     |     | 36   |
| N                          |              | 1   |     |     |     |     |      | 3   |     | 255  |
| P                          |              | 1   |     | 1   |     |     |      |     |     | 1147 |
| Q                          |              |     | 1   |     | 1   |     |      |     |     | 1314 |
| R                          |              |     | 9   |     |     | 2   |      | 4   | 134 | 1326 |
| S                          |              | 2   |     |     |     |     |      |     |     | 2629 |
| T                          |              | 162 | 1   |     |     |     |      | 1   |     | 1593 |
| V                          |              |     |     | 111 |     | 11  |      |     |     | 646  |
| W                          |              |     |     |     |     |     |      |     |     | 287  |
| X                          |              |     |     |     |     |     |      |     |     |      |
| Y                          |              |     | 1   |     |     |     |      |     |     | 1014 |
| -                          | 1            | 1   | 1   | 1   | 1   | 1   | 166  | 1   | 1   | 2151 |
| unknown (?)                |              |     |     |     |     |     |      |     |     | 4    |
| not sequenced <sup>2</sup> | 16           | 16  | 15  | 16  | 16  | 16  | 17   | 17  | 45  | 337  |
| sum of seq <sup>3</sup>    | 167          | 167 | 168 | 167 | 167 | 167 | 166  | 166 | 138 |      |
| oomcaa <sup>4</sup>        | 166          | 162 | 152 | 111 | 141 | 143 | 166  | 157 | 134 |      |
| mcaa <sup>5</sup>          | G            | T   | K   | V   | E   | I   | -    | K   | R   |      |
| rel. oomcaa <sup>6</sup>   | 99%          | 97% | 90% | 66% | 84% | 86% | 100% | 95% | 97% |      |
| pos occupied <sup>6</sup>  | 2            | 5   | 7   | 4   | 5   | 7   | 1    | 5   | 4   |      |

Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | Framework I |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
|---------------------------|-------------|------|-----|-----|------|-----|------|------|------|-----|------|-----|------|------|------|-----|-----|------|
|                           | 1           | 2    | 3   | 4   | 5    | 6   | 7    | 8    | 9    | 10  | 11   | 12  | 13   | 14   | 15   | 16  | 17  | 18   |
| A                         |             |      |     |     |      |     |      |      |      |     |      | 24  |      |      |      |     | 1   |      |
| B                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| C                         |             |      |     |     |      |     |      |      |      | 1   |      |     |      |      |      | 1   |     |      |
| D                         | 25          |      |     |     |      |     |      |      | 26   |     |      |     |      |      |      |     |     |      |
| E                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     | 25  |      |
| F                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| G                         |             |      |     |     |      |     |      |      |      |     |      | 1   |      |      |      | 24  |     |      |
| H                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| I                         |             | 26   |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| K                         |             |      |     |     |      | 1   |      |      |      |     |      |     |      |      |      |     |     |      |
| L                         |             |      |     | 1   |      |     |      |      |      | 26  |      |     |      |      | 26   |     |     |      |
| M                         |             |      |     | 24  |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| N                         | 1           |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| P                         |             |      |     |     |      |     |      | 26   |      |     |      | 1   |      |      |      |     |     |      |
| Q                         |             |      | 1   |     |      | 25  |      |      |      |     |      |     |      |      |      |     |     |      |
| R                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     | 26   |
| S                         |             |      |     |     |      |     | 26   |      |      | 25  |      |     |      | 26   |      | 1   |     |      |
| T                         |             |      |     |     | 26   |     |      |      |      |     |      |     |      |      |      |     |     |      |
| V                         |             |      | 25  | 1   |      |     |      |      |      |     |      |     | 26   |      |      |     |     |      |
| W                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| X                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| Y                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| -                         |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| unknown (?)               |             |      |     |     |      |     |      |      |      |     |      |     |      |      |      |     |     |      |
| not sequenced             | 7           | 7    | 7   | 7   | 7    | 7   | 7    | 7    | 7    | 7   | 7    | 7   | 7    | 7    | 7    | 7   | 7   | 7    |
| sum of seq <sup>2</sup>   | 26          | 26   | 26  | 26  | 26   | 26  | 26   | 26   | 26   | 26  | 26   | 26  | 26   | 26   | 26   | 26  | 26  | 26   |
| oomcaa <sup>3</sup>       | 25          | 26   | 25  | 24  | 26   | 25  | 26   | 26   | 26   | 25  | 26   | 24  | 26   | 26   | 26   | 24  | 25  | 26   |
| mcaa <sup>4</sup>         | D           | I    | V   | M   | T    | Q   | S    | P    | D    | S   | L    | A   | V    | S    | L    | G   | E   | R    |
| rel. oomcaa <sup>5</sup>  | 96%         | 100% | 96% | 92% | 100% | 96% | 100% | 100% | 100% | 96% | 100% | 92% | 100% | 100% | 100% | 92% | 96% | 100% |
| pos occupied <sup>6</sup> | 2           | 1    | 2   | 3   | 1    | 2   | 1    | 1    | 1    | 2   | 1    | 3   | 1    | 1    | 1    | 3   | 2   | 1    |



Table 4D: Analysis of V kappa subgroup 4

4D: Analysis of V kappa subgroup 4

|                           | CDRI |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
|---------------------------|------|------|------|------|------|------|-----|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|--|
| amino acid <sup>1</sup>   | 19   | 20   | 21   | 22   | 23   | 24   | 25  | 26   | 27  | A    | B   | C   | D   | E   | F   | 28  | 29  | 30  |  |
| A                         | 26   |      |      |      |      |      | 1   |      |     |      | 1   |     |     |     |     |     |     |     |  |
| B                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| C                         |      |      |      |      | 33   |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| D                         |      |      |      |      |      |      |     |      |     |      | 1   |     | 1   |     |     | 1   |     |     |  |
| E                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| F                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| G                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| H                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| I                         |      |      | 26   |      |      |      |     |      |     |      | 1   |     |     |     |     |     |     |     |  |
| K                         |      |      |      |      |      | 33   |     |      |     |      |     |     |     |     |     | 2   |     | 30  |  |
| L                         |      |      |      |      |      |      |     |      |     |      | 2   | 31  |     |     |     |     |     |     |  |
| M                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| N                         |      |      |      | 26   |      |      |     |      |     |      |     |     |     |     |     | 30  | 31  | 1   |  |
| P                         |      |      |      |      |      |      | 1   |      |     |      |     |     |     |     | 1   |     |     |     |  |
| Q                         |      |      |      |      |      |      |     |      | 32  |      |     |     |     |     |     |     |     | 1   |  |
| R                         |      |      |      |      |      |      |     |      | 1   |      |     |     |     |     |     |     | 1   | 1   |  |
| S                         |      |      |      |      |      |      | 31  | 33   |     | 33   |     |     |     | 32  | 32  |     | 1   |     |  |
| T                         |      | 26   |      |      |      |      |     |      |     |      |     |     |     | 1   |     |     |     |     |  |
| V                         |      |      |      |      |      |      |     |      |     |      | 28  | 2   |     |     |     |     |     |     |  |
| W                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| X                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| Y                         |      |      |      |      |      |      |     |      |     |      |     |     | 32  |     |     |     |     |     |  |
| -                         |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| unknown (?)               |      |      |      |      |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| not sequenced             | 7    | 7    | 7    | 7    |      |      |     |      |     |      |     |     |     |     |     |     |     |     |  |
| sum of seq <sup>2</sup>   | 26   | 26   | 26   | 26   | 33   | 33   | 33  | 33   | 33  | 33   | 33  | 33  | 33  | 33  | 33  | 33  | 33  | 33  |  |
| oomcaa <sup>3</sup>       | 26   | 26   | 26   | 26   | 33   | 33   | 31  | 33   | 32  | 33   | 28  | 31  | 32  | 32  | 32  | 30  | 31  | 30  |  |
| mcaa <sup>4</sup>         | A    | T    | I    | N    | C    | K    | S   | S    | Q   | S    | V   | L   | Y   | S   | S   | N   | N   | K   |  |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 100% | 100% | 100% | 100% | 94% | 100% | 97% | 100% | 85% | 94% | 97% | 97% | 97% | 91% | 94% | 91% |  |
| pos occupied <sup>6</sup> | 1    | 1    | 1    | 1    | 1    | 1    | 3   | 1    | 2   | 1    | 5   | 2   | 2   | 2   | 2   | 3   | 3   | 4   |  |

Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | Framework II |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
|---------------------------|--------------|------|------|-----|------|-----|-----|------|------|-----|-----|-----|-----|------|-----|-----|------|-----|
|                           | 31           | 32   | 33   | 34  | 35   | 36  | 37  | 38   | 39   | 40  | 41  | 42  | 43  | 44   | 45  | 46  | 47   | 48  |
| A                         |              |      |      | 32  |      |     |     |      |      | 2   |     |     |     |      |     |     |      |     |
| B                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| C                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| D                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| E                         |              |      |      |     |      |     |     |      |      |     | 1   |     |     |      |     |     |      |     |
| F                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| G                         |              |      |      |     |      |     |     |      |      | 32  |     |     |     |      |     |     |      |     |
| H                         |              |      |      |     |      | 2   |     |      |      |     |     |     |     |      |     |     |      |     |
| I                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      | 32  |
| K                         |              |      |      |     |      |     |     |      | 33   |     |     |     |     |      | 32  |     |      |     |
| L                         |              |      | 33   |     |      |     |     |      |      |     |     |     |     |      |     | 29  | 33   |     |
| M                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      | 1   |
| N                         | 33           |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| P                         |              |      |      |     |      |     |     |      |      | 31  |     |     | 31  | 33   |     |     |      |     |
| Q                         |              |      |      |     |      |     | 32  | 33   |      |     |     | 32  |     |      |     |     |      |     |
| R                         |              |      |      |     |      |     | 1   |      |      |     |     | 1   |     |      |     | 1   |      |     |
| S                         |              |      |      |     |      |     |     |      |      |     |     |     | 2   |      |     |     |      |     |
| T                         |              |      |      | 1   |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| V                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     | 4   |      |     |
| W                         |              |      |      |     | 33   |     |     |      |      |     |     |     |     |      |     |     |      |     |
| X                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| Y                         |              | 33   |      |     |      | 31  |     |      |      |     |     |     |     |      |     |     |      |     |
| -                         |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| unknown (?)               |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| not sequenced             |              |      |      |     |      |     |     |      |      |     |     |     |     |      |     |     |      |     |
| sum of seq <sup>2</sup>   | 33           | 33   | 33   | 33  | 33   | 33  | 33  | 33   | 33   | 33  | 33  | 33  | 33  | 33   | 33  | 33  | 33   | 33  |
| oomcaa <sup>3</sup>       | 33           | 33   | 33   | 32  | 33   | 31  | 32  | 33   | 33   | 31  | 32  | 32  | 31  | 33   | 32  | 29  | 33   | 32  |
| mcaa <sup>4</sup>         | N            | Y    | L    | A   | W    | Y   | Q   | Q    | K    | P   | G   | Q   | P   | P    | K   | L   | L    | I   |
| rel. oomcaa <sup>5</sup>  | 100%         | 100% | 100% | 97% | 100% | 94% | 97% | 100% | 100% | 94% | 97% | 97% | 94% | 100% | 97% | 88% | 100% | 97% |
| pos occupied <sup>6</sup> | 1            | 1    | 1    | 2   | 1    | 2   | 2   | 1    | 1    | 2   | 2   | 2   | 2   | 1    | 2   | 2   | 1    | 2   |

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Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | CDR II |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
|---------------------------|--------|------|-----|-----|-----|------|-----|------|------|------|------|------|-----|------|-----|------|------|------|
|                           | 49     | 50   | 51  | 52  | 53  | 54   | 55  | 56   | 57   | 58   | 59   | 60   | 61  | 62   | 63  | 64   | 65   | 66   |
| A                         |        |      | 30  |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| B                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| C                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| D                         |        |      |     |     |     |      |     |      |      |      |      | 33   |     |      |     |      |      |      |
| E                         |        |      |     |     |     |      | 32  |      |      |      |      |      |     |      |     |      |      |      |
| F                         |        |      |     |     |     |      |     |      |      |      |      |      |     | 33   |     |      |      |      |
| G                         |        |      |     |     |     |      |     |      | 33   |      |      |      |     |      | 1   | 33   |      | 33   |
| H                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| I                         |        |      |     |     | 1   |      |     |      |      |      |      |      |     |      |     |      |      |      |
| K                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| L                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| M                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| N                         |        |      |     |     | 2   |      |     |      |      |      |      |      |     |      |     |      |      |      |
| P                         |        |      |     | 1   |     |      |     |      |      |      |      | 33   |     | 1    |     |      |      |      |
| Q                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| R                         |        |      |     |     |     | 33   |     |      |      |      |      |      |     | 32   |     |      |      |      |
| S                         |        |      | 1   | 31  | 1   |      |     | 33   |      |      |      |      |     |      | 32  |      | 33   |      |
| T                         |        |      | 2   | 1   | 29  |      |     |      |      |      |      |      |     |      |     |      |      |      |
| V                         |        |      |     |     |     |      | 1   |      |      | 33   |      |      |     |      |     |      |      |      |
| W                         |        | 33   |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| X                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| Y                         | 33     |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| -                         |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| unknown (?)               |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| not sequenced             |        |      |     |     |     |      |     |      |      |      |      |      |     |      |     |      |      |      |
| sum of seq <sup>2</sup>   | 33     | 33   | 33  | 33  | 33  | 33   | 33  | 33   | 33   | 33   | 33   | 33   | 33  | 33   | 33  | 33   | 33   | 33   |
| oomcaa <sup>1</sup>       | 33     | 33   | 30  | 31  | 29  | 33   | 32  | 33   | 33   | 33   | 33   | 33   | 33  | 32   | 33  | 32   | 33   | 33   |
| mcaa <sup>1</sup>         | Y      | W    | A   | S   | T   | R    | E   | S    | G    | V    | P    | D    | R   | F    | S   | G    | S    | G    |
| rel. oomcaa <sup>1</sup>  | 100%   | 100% | 91% | 94% | 88% | 100% | 97% | 100% | 100% | 100% | 100% | 100% | 97% | 100% | 97% | 100% | 100% | 100% |
| pos occupied <sup>1</sup> | 1      | 1    | 3   | 3   | 4   | 1    | 2   | 1    | 1    | 1    | 1    | 1    | 1   | 2    | 1   | 2    | 1    | 1    |

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Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | Framework III |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
|---------------------------|---------------|------|------|-----|-----|------|------|------|------|-----|-----|-----|-----|------|------|------|------|-----|
|                           | 67            | 68   | 69   | 70  | 71  | 72   | 73   | 74   | 75   | 76  | 77  | 78  | 79  | 80   | 81   | 82   | 83   | 84  |
| A                         |               |      |      |     |     |      |      |      |      |     |     |     |     | 33   |      |      |      | 32  |
| B                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| C                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| D                         |               |      |      | 32  |     |      |      |      |      |     |     |     |     |      |      | 33   |      |     |
| E                         |               |      |      |     |     |      |      |      |      |     |     |     |     | 33   |      |      |      |     |
| F                         |               |      |      |     | 32  |      |      |      |      |     |     |     |     |      |      |      |      |     |
| G                         |               | 33   |      | 1   |     |      |      |      |      |     |     |     |     |      |      |      |      | 1   |
| H                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| I                         |               |      |      |     |     |      |      |      | 33   |     |     |     |     |      |      |      |      |     |
| K                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| L                         |               |      |      |     |     |      | 33   |      |      |     |     | 32  |     |      |      |      |      |     |
| M                         |               |      |      |     |     |      |      |      |      |     |     |     | 1   |      |      |      |      |     |
| N                         |               |      |      |     |     |      |      |      |      | 2   | 1   |     |     |      |      |      |      |     |
| P                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| Q                         |               |      |      |     |     |      |      |      |      |     |     |     | 32  |      |      |      |      |     |
| R                         |               |      |      |     |     |      |      |      |      |     |     |     | 1   |      |      |      |      |     |
| S                         | 33            |      |      |     |     |      |      |      |      | 30  | 32  |     |     |      |      |      |      |     |
| T                         |               | 33   |      |     | 33  |      | 33   |      |      | 1   |     |     |     |      |      |      |      |     |
| V                         |               |      |      |     | 1   |      |      |      |      |     |     |     |     |      |      |      | 33   |     |
| W                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| X                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| Y                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| -                         |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| unknown (?)               |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| not sequenced             |               |      |      |     |     |      |      |      |      |     |     |     |     |      |      |      |      |     |
| sum of seq <sup>2</sup>   | 33            | 33   | 33   | 33  | 33  | 33   | 33   | 33   | 33   | 33  | 33  | 33  | 33  | 33   | 33   | 33   | 33   | 33  |
| oomcaa <sup>3</sup>       | 33            | 33   | 33   | 32  | 32  | 33   | 33   | 33   | 33   | 30  | 32  | 32  | 32  | 33   | 33   | 33   | 33   | 32  |
| mcaa <sup>4</sup>         | S             | G    | T    | D   | F   | T    | L    | T    | I    | S   | S   | L   | Q   | A    | E    | D    | V    | A   |
| rel. oomcaa <sup>5</sup>  | 100%          | 100% | 100% | 97% | 97% | 100% | 100% | 100% | 100% | 91% | 97% | 97% | 97% | 100% | 100% | 100% | 100% | 97% |
| pos occupied <sup>6</sup> | 1             | 1    | 1    | 2   | 2   | 1    | 1    | 1    | 1    | 3   | 2   | 2   | 2   | 1    | 1    | 1    | 1    | 2   |

Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | CDR III |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
|---------------------------|---------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|
|                           | 85      | 86   | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B    | C    | D    | E   |
| A                         |         |      |     |      |     |     |     |     |     | 1   |     |     |      |      |      |     |
| B                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| C                         |         |      |     | 33   |     |     |     |     |     |     |     |     |      |      |      |     |
| D                         |         |      |     |      |     |     |     | 1   | 1   |     |     |     |      |      |      |     |
| E                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| F                         |         |      | 1   |      |     |     |     | 1   |     |     |     |     |      |      |      |     |
| G                         |         |      |     |      |     |     |     |     | 2   | -   |     |     |      |      |      |     |
| H                         |         |      | 1   |      | 3   |     |     |     |     |     |     |     |      |      |      |     |
| I                         |         |      |     |      |     |     |     |     |     | 2   |     |     |      |      |      |     |
| K                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| L                         |         |      |     |      |     | 1   |     | 2   |     | 1   | 3   |     |      |      |      | 1   |
| M                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| N                         |         |      |     |      |     |     |     |     | 4   | 4   |     |     |      |      |      |     |
| P                         |         |      |     |      |     |     |     |     |     | 1   | 29  | 1   |      |      |      | 4   |
| Q                         |         |      |     |      | 30  | 32  |     |     |     |     | 1   |     |      |      |      | 1   |
| R                         |         |      |     |      |     |     |     |     | 1   |     |     | 1   |      |      |      | 2   |
| S                         |         |      |     |      |     |     | 2   | 23  | 2   |     |     |     |      |      |      | 1   |
| T                         |         |      |     |      |     |     |     | 2   | 22  |     |     |     |      |      |      |     |
| V                         | 33      |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| W                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      | 2   |
| X                         |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| Y                         |         | 33   | 31  |      |     |     | 31  | 29  |     |     |     |     |      |      |      | 1   |
| -                         |         |      |     |      |     |     |     |     |     |     |     | 13  | 15   | 15   | 15   | 15  |
| unknown (?)               |         |      |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| not sequenced             |         |      |     |      |     |     |     |     |     |     |     | 18  | 18   | 18   | 18   | 18  |
| sum of seq <sup>2</sup>   | 33      | 33   | 33  | 33   | 33  | 33  | 33  | 33  | 33  | 33  | 33  | 15  | 15   | 15   | 15   | 15  |
| oomcaa <sup>3</sup>       | 33      | 33   | 31  | 33   | 30  | 32  | 31  | 29  | 23  | 22  | 29  | 13  | 15   | 15   | 15   | 4   |
| mcaa <sup>4</sup>         | V       | Y    | Y   | C    | Q   | Q   | Y   | Y   | S   | T   | P   | -   | -    | -    | -    | P   |
| rel. oomcaa <sup>5</sup>  | 100%    | 100% | 94% | 100% | 91% | 97% | 94% | 88% | 70% | 67% | 88% | 87% | 100% | 100% | 100% | 27% |
| pos occupied <sup>6</sup> | 1       | 1    | 3   | 1    | 2   | 2   | 2   | 4   | 6   | 7   | 3   | 3   | 1    | 1    | 1    | 8   |

Table 4D: Analysis of V kappa subgroup 4

| amino acid <sup>1</sup>   | Framework IV |      |      |     |      |     |     |     |     |     |      |     |      | sum |
|---------------------------|--------------|------|------|-----|------|-----|-----|-----|-----|-----|------|-----|------|-----|
|                           | 97           | 98   | 99   | 100 | 101  | 102 | 103 | 104 | 105 | 106 | A    | 107 | 108  |     |
| A                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 183 |
| B                         |              |      |      |     |      |     |     |     |     |     |      |     |      |     |
| C                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 68  |
| D                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 154 |
| E                         |              |      |      |     |      |     |     |     | 14  |     |      |     |      | 105 |
| F                         |              | 15   |      |     |      |     |     |     |     |     |      |     |      | 82  |
| G                         |              |      | 15   | 4   | 15   |     |     |     |     |     |      |     |      | 228 |
| H                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 6   |
| I                         |              |      |      |     |      |     |     |     |     | 14  |      |     |      | 135 |
| K                         |              |      |      |     |      |     | 14  |     |     |     |      | 13  |      | 158 |
| L                         |              |      |      |     |      |     |     | 4   |     |     |      |     |      | 258 |
| M                         | 1            |      |      |     |      |     |     |     |     |     |      |     |      | 27  |
| N                         |              |      |      |     |      |     |     |     |     |     |      | 1   |      | 136 |
| P                         |              |      |      |     |      | 1   |     |     |     |     |      |     |      | 195 |
| Q                         |              |      |      | 11  |      |     |     | 1   |     |     |      |     |      | 264 |
| R                         |              |      |      |     |      |     | 1   |     | 1   |     |      | 1   | 11   | 116 |
| S                         | 2            |      |      |     |      |     |     |     |     | 1   |      |     |      | 499 |
| T                         | 12           |      |      |     |      | 14  |     |     |     |     |      |     |      | 236 |
| V                         |              |      |      |     |      |     |     | 9   |     |     |      |     |      | 196 |
| W                         |              |      |      |     |      |     |     | 1   |     |     |      |     |      | 69  |
| X                         |              |      |      |     |      |     |     |     |     |     |      |     |      |     |
| Y                         |              |      |      |     |      |     |     |     |     |     |      |     |      | 254 |
| -                         |              |      |      |     |      |     |     |     |     |     | 15   |     |      | 106 |
| unknown (?)               |              |      |      |     |      |     |     |     |     |     |      |     |      |     |
| not sequenced             | 18           | 18   | 18   | 18  | 18   | 18  | 18  | 18  | 18  | 18  | 18   | 18  | 22   | 518 |
| sum of seq <sup>2</sup>   | 15           | 15   | 15   | 15  | 15   | 15  | 15  | 15  | 15  | 15  | 15   | 15  | 11   |     |
| oomcaa <sup>3</sup>       | 12           | 15   | 15   | 11  | 15   | 14  | 14  | 9   | 14  | 14  | 15   | 13  | 11   |     |
| mcaa <sup>4</sup>         | T            | F    | G    | Q   | G    | T   | K   | V   | E   | I   | -    | K   | R    |     |
| rel. oomcaa <sup>5</sup>  | 80%          | 100% | 100% | 73% | 100% | 93% | 93% | 60% | 93% | 93% | 100% | 87% | 100% |     |
| pos occupied <sup>6</sup> | 3            | 1    | 1    | 2   | 1    | 2   | 2   | 4   | 2   | 2   | 1    | 3   | 1    |     |

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Table 5A: Analysis of V lambda subgroup 1

| Framework I               |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
|---------------------------|-----|-----|-----|------|------|------|------|------|------|------|-----|------|-----|-----|-----|------|------|-----|------|
| amino acid <sup>1</sup>   | 1   | 2   | 3   | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11  | 12   | 13  | 14  | 15  | 16   | 17   | 18  | 19   |
| A                         |     |     |     |      |      |      |      |      |      |      | 19  |      | 18  | 20  |     |      |      |     |      |
| B                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| C                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| D                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| E                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      | 1   |      |
| F                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| G                         |     |     |     |      |      |      |      |      |      |      |     |      | 22  |     |     | 42   |      |     |      |
| H                         | 2   |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| I                         |     |     | 1   |      |      |      |      |      |      |      | 1   |      |     |     |     |      |      |     |      |
| K                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      | 14  |      |
| L                         |     |     | 1   | 41   |      |      |      |      |      |      | 1   |      |     |     |     |      |      |     |      |
| M                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| N                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| P                         |     |     |     |      |      |      | 41   | 41   |      |      |     |      |     | 1   | 41  |      |      |     |      |
| Q                         | 22  |     | 1   |      |      | 41   |      |      |      |      |     |      |     |     |     |      | 42   |     |      |
| R                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      | 25  |      |
| S                         |     | 39  |     |      |      |      |      |      | 41   |      |     | 41   |     |     | 1   |      |      | 1   |      |
| T                         |     |     |     |      | 41   |      |      |      |      |      |     |      |     | 19  |     |      |      | 1   |      |
| V                         |     | 1   | 38  |      |      |      |      |      |      |      | 20  |      | 1   | 1   |     |      |      |     | 42   |
| W                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| X                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| Y                         |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| Z                         | 16  |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| -                         |     |     |     |      |      |      |      |      |      | 41   |     |      |     |     |     |      |      |     |      |
| unknown (?)               |     |     |     |      |      |      |      |      |      |      |     |      |     |     |     |      |      |     |      |
| not sequenced             | 2   | 2   | 1   | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   | 1    | 1   | 1   |     |      |      |     |      |
| sum of seq <sup>2</sup>   | 40  | 40  | 41  | 41   | 41   | 41   | 41   | 41   | 41   | 41   | 41  | 41   | 41  | 41  | 42  | 42   | 42   | 42  | 42   |
| oomcaa <sup>3</sup>       | 22  | 39  | 38  | 41   | 41   | 41   | 41   | 41   | 41   | 41   | 20  | 41   | 22  | 20  | 41  | 42   | 42   | 25  | 42   |
| mcaa <sup>4</sup>         | Q   | S   | V   | L    | T    | Q    | P    | P    | S    | -    | V   | S    | G   | A   | P   | G    | Q    | R   | V    |
| rel. oomcaa <sup>5</sup>  | 55% | 98% | 93% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 49% | 100% | 54% | 49% | 98% | 100% | 100% | 60% | 100% |
| pos occupied <sup>6</sup> | 3   | 2   | 4   | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 4   | 1    | 3   | 4   | 2   | 1    | 1    | 5   | 1    |

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Table 5A: Analysis of V lambda subgroup 1

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|                           | CDRI |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
|---------------------------|------|-----|------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--|--|--|---|----|--|
| amino acid <sup>1</sup>   | 20   | 21  | 22   | 23   | 24  | 25   | 26  | 27  | D   | E   | 28  | 29  | 30  | 31  | A   | 32  | 33  | 34  | 35   |  |  |  |   |    |  |
| A                         | 2    |     |      |      |     |      |     | 1   |     |     |     |     | 2   | 2   |     |     | 1   |     |      |  |  |  |   |    |  |
| B                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
| C                         |      |     |      | 42   |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
| D                         |      |     |      |      |     |      |     |     |     | 3   |     |     | 3   | 1   |     | 3   |     |     | 1    |  |  |  |   |    |  |
| E                         |      |     |      |      |     |      |     |     |     |     |     |     | 1   |     |     |     |     |     |      |  |  |  |   |    |  |
| F                         |      |     |      |      | 1   |      |     |     | 1   |     |     |     |     |     |     | 1   | 1   |     |      |  |  |  |   |    |  |
| G                         |      |     |      |      | 42  | 3    | 1   |     |     |     | 2   | 39  | 4   | 2   |     |     |     |     |      |  |  |  |   |    |  |
| H                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 2   |     | 2   |     |      |  |  |  | 2 |    |  |
| I                         | 1    | 41  |      |      |     |      |     |     |     | 1   | 37  |     |     |     |     |     |     |     |      |  |  |  | 1 |    |  |
| K                         |      |     |      |      |     |      |     |     |     | 1   |     |     |     | 1   |     |     |     |     |      |  |  |  |   |    |  |
| L                         |      | 1   |      |      |     |      |     |     |     |     | 1   |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
| M                         |      |     |      |      |     |      |     |     |     |     | 1   |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
| N                         |      |     |      |      |     |      |     | 2   | 1   | 37  |     |     | 13  | 31  | 2   |     | 1   |     | 9    |  |  |  |   |    |  |
| P                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     | 1   |     |     |      |  |  |  |   |    |  |
| Q                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     | 1   |     |     |      |  |  |  |   |    |  |
| R                         |      |     |      |      |     |      | 1   | 1   |     |     |     |     | 5   |     |     |     |     |     |      |  |  |  |   |    |  |
| S                         | 1    | 42  |      | 38   | 34  | 34   | 38  |     |     |     |     |     | 13  | 1   | 1   | 3   |     | 19  |      |  |  |  |   |    |  |
| T                         | 38   |     |      | 3    |     | 4    | 3   | 2   |     |     |     | 1   |     | 1   |     | 7   |     | 2   |      |  |  |  |   |    |  |
| V                         |      |     |      |      |     |      |     |     |     |     | 1   |     |     |     |     | 2   | 40  |     |      |  |  |  |   |    |  |
| W                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |   | 42 |  |
| X                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
| Y                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 4   | 1   | 20  |     | 7    |  |  |  |   |    |  |
| Z                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
| -                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 36  |     |     |     |      |  |  |  |   |    |  |
| unknown (?)               |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |   |    |  |
| not sequenced             |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 1   | 1   | 1   | 1   |      |  |  |  |   |    |  |
| sum of seq <sup>2</sup>   | 42   | 42  | 42   | 42   | 42  | 42   | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 41  | 41  | 41  | 41  | 42   |  |  |  |   |    |  |
| oomcaa <sup>3</sup>       | 38   | 41  | 42   | 42   | 38  | 42   | 34  | 34  | 38  | 37  | 37  | 39  | 13  | 31  | 36  | 20  | 40  | 19  | 42   |  |  |  |   |    |  |
| mcaa <sup>4</sup>         | T    | I   | S    | C    | S   | G    | S   | S   | S   | N   | I   | G   | N   | N   | -   | Y   | V   | S   | W    |  |  |  |   |    |  |
| rel. oomcaa <sup>5</sup>  | 90%  | 98% | 100% | 100% | 90% | 100% | 81% | 81% | 90% | 88% | 88% | 93% | 31% | 74% | 88% | 49% | 98% | 46% | 100% |  |  |  |   |    |  |
| pos occupied <sup>6</sup> | 4    | 2   | 1    | 1    | 3   | 1    | 4   | 6   | 4   | 4   | 5   | 3   | 8   | 7   | 5   | 10  | 2   | 7   | 1    |  |  |  |   |    |  |



Table 5A: Analysis of V lambda subgroup 1

| amino acid <sup>1</sup>   | Framework II |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
|---------------------------|--------------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
|                           | 36           | 37  | 38  | 39  | 40   | 41  | 42  | 43  | 44   | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52  | 53  | 54  |     |    |    |    |    |
| A                         |              |     |     |     |      |     | 4   | 40  |      |     |     |     |     |     |     |     |     | 1   |     |     |    |    |    |    |
| B                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| C                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| D                         |              |     |     |     |      | 1   |     |     |      |     |     |     |     |     | 13  | 10  | 8   |     |     |     |    |    |    |    |
| E                         |              |     |     |     |      |     |     |     |      | 2   |     |     |     |     | 5   |     |     | 1   |     |     |    |    |    |    |
| F                         | 1            |     |     | 4   |      |     |     |     |      |     |     |     |     | 1   |     |     |     |     |     |     |    |    |    |    |
| G                         |              |     |     |     |      | 39  |     |     |      |     |     |     |     |     | 1   |     |     |     |     |     |    |    |    |    |
| H                         | 1            | 1   | 6   | 1   |      |     |     |     |      |     |     |     |     | 1   |     |     |     |     | 1   |     |    |    |    |    |
| I                         |              |     |     |     |      |     |     |     |      |     |     |     | 40  |     | 1   |     |     |     |     |     |    |    |    |    |
| K                         |              |     |     |     |      |     | 1   |     |      | 35  |     |     |     |     | 1   | 1   |     | 18  |     |     |    |    |    |    |
| L                         |              |     | 1   | 31  |      |     |     |     |      |     | 41  | 40  |     |     |     |     |     | 1   | 1   |     |    |    |    |    |
| M                         |              |     |     |     |      |     | 1   |     |      |     |     |     |     | 1   |     |     |     |     | 1   |     |    |    |    |    |
| N                         |              |     |     |     |      |     |     |     |      | 1   |     |     |     |     | 3   | 28  | 30  | 2   |     |     |    |    |    |    |
| P                         |              |     |     |     | 42   | 1   |     |     | 42   |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| Q                         |              | 39  | 34  |     |      |     |     |     |      |     |     |     |     |     |     |     |     | 15  |     |     |    |    |    |    |
| R                         |              | 2   |     | 1   |      | 1   |     |     |      | 4   |     |     |     |     | 7   |     |     | 2   | 40  |     |    |    |    |    |
| S                         |              |     |     |     |      |     |     | 1   |      |     |     |     |     |     | 9   | 2   | 3   | 1   |     |     |    |    |    |    |
| T                         |              |     |     |     |      |     | 36  | 1   |      |     |     |     |     |     | 1   |     |     |     |     |     |    |    |    |    |
| V                         |              |     | 1   | 5   |      |     |     |     |      |     | 1   | 2   | 1   |     |     |     |     |     |     |     |    |    |    |    |
| W                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     | 1   |     |    |    |    |    |
| X                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| Y                         | 40           |     |     |     |      |     |     |     |      |     |     |     |     | 40  | 1   | 1   |     |     |     |     |    |    |    |    |
| Z                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| -                         |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| unknown (?)               |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| not sequenced             |              |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
| sum of seq <sup>1</sup>   | 42           | 42  | 42  | 42  | 42   | 42  | 42  | 42  | 42   | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42  | 42 | 42 | 42 | 42 |
| oomcaa <sup>1</sup>       | 40           | 39  | 34  | 31  | 42   | 39  | 36  | 40  | 42   | 35  | 41  | 40  | 40  | 40  | 40  | 13  | 28  | 30  | 18  | 40  |    |    |    |    |
| mcaa <sup>1</sup>         | Y            | Q   | Q   | L   | P    | G   | T   | A   | P    | K   | L   | L   | I   | Y   | D   | N   | N   | K   | R   |     |    |    |    |    |
| rel. oomcaa <sup>1</sup>  | 95%          | 93% | 81% | 74% | 100% | 93% | 86% | 95% | 100% | 83% | 98% | 95% | 95% | 95% | 95% | 31% | 67% | 71% | 43% | 95% |    |    |    |    |
| pos occupied <sup>1</sup> | 3            | 3   | 4   | 5   | 1    | 4   | 4   | 3   | 1    | 4   | 2   | 2   | 3   | 3   | 10  | 5   | 4   | 9   | 3   |     |    |    |    |    |

Table 5A: Analysis of V lambda subgroup 1

|                           |     | CDR II |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
|---------------------------|-----|--------|------|------|------|------|------|------|-----|-----|-----|------|-----|------|-----|------|-----|------|------|--|--|
| amino acid <sup>1</sup>   | 55  | 56     | A    | B    | C    | D    | E    | 57   | 58  | 59  | 60  | 61   | 62  | 63   | 64  | 65   | 66  | A    | B    |  |  |
| A                         | 1   |        |      |      |      |      |      |      |     |     |     |      |     |      | 5   |      |     |      |      |  |  |
| B                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| C                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| D                         |     |        |      |      |      |      |      |      |     |     | 38  |      |     |      |     |      |     |      |      |  |  |
| E                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| F                         |     |        |      |      |      |      |      |      |     |     |     |      | 38  |      |     |      |     |      |      |  |  |
| G                         |     |        |      |      |      |      |      | 41   |     |     | 2   |      |     |      | 36  |      |     |      |      |  |  |
| H                         |     |        |      |      |      |      |      |      |     |     | 1   |      |     |      |     |      |     |      |      |  |  |
| I                         |     |        |      |      |      |      |      |      | 17  |     |     |      | 3   |      |     |      |     |      |      |  |  |
| K                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      | 38  |      |      |  |  |
| L                         |     | 1      |      |      |      |      |      |      |     | 1   |     |      |     |      |     |      |     |      |      |  |  |
| M                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| N                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| P                         | 38  |        |      |      |      |      |      |      |     | 38  |     |      |     |      |     |      |     |      |      |  |  |
| Q                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| R                         |     |        |      |      |      |      |      |      |     |     |     | 42   |     |      |     |      | 4   |      |      |  |  |
| S                         | 2   | 40     |      |      |      |      |      |      |     | 2   |     |      |     | 42   |     | 42   |     |      |      |  |  |
| T                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      | 1   |      |     |      |      |  |  |
| V                         |     |        |      |      |      |      |      |      | 24  |     |     |      | 1   |      |     |      |     |      |      |  |  |
| W                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| X                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| Y                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| Z                         |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| -                         |     |        | 41   | 41   | 41   | 41   | 42   |      |     |     |     |      |     |      |     |      |     | 42   | 42   |  |  |
| unknown (?)               |     |        |      |      |      |      |      |      |     |     |     |      |     |      |     |      |     |      |      |  |  |
| not sequenced             | 1   | 1      |      |      |      |      |      | 1    | 1   | 1   | 1   |      |     |      |     |      |     |      |      |  |  |
| sum of seq <sup>2</sup>   | 41  | 41     | 41   | 41   | 41   | 41   | 42   | 41   | 41  | 41  | 41  | 42   | 42  | 42   | 42  | 42   | 42  | 42   | 42   |  |  |
| oomcaa <sup>3</sup>       | 38  | 40     | 41   | 41   | 41   | 41   | 42   | 41   | 24  | 38  | 38  | 42   | 38  | 42   | 36  | 42   | 38  | 42   | 42   |  |  |
| mcaa <sup>4</sup>         | P   | S      | -    | -    | -    | -    | -    | G    | V   | P   | D   | R    | F   | S    | G   | S    | K   | -    | -    |  |  |
| rel. oomcaa <sup>5</sup>  | 93% | 98%    | 100% | 100% | 100% | 100% | 100% | 100% | 59% | 93% | 93% | 100% | 90% | 100% | 86% | 100% | 90% | 100% | 100% |  |  |
| pos occupied <sup>6</sup> | 3   | 2      | 1    | 1    | 1    | 1    | 1    | 1    | 2   | 3   | 3   | 1    | 3   | 1    | 3   | 1    | 2   | 1    | 1    |  |  |

Table 5A: Analysis of V lambda subgroup 1

| amino acid <sup>1</sup>   | Framework III |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
|---------------------------|---------------|-----|-----|------|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|------|-----|-----|
|                           | 67            | 68  | 69  | 70   | 71  | 72  | 73   | 74  | 75  | 76  | 77   | 78  | 79  | 80  | 81  | 82  | 83   | 84  | 85  |
| A                         |               | 1   | 3   |      | 41  |     |      | 24  |     |     |      |     |     | 2   |     |     |      | 38  | 1   |
| B                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| C                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| D                         |               | 1   |     |      |     |     |      |     |     |     |      |     |     |     | 1   | 41  |      |     | 37  |
| E                         |               |     |     |      |     |     |      |     |     |     |      |     | 1   |     | 24  |     | 42   |     | 1   |
| F                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| G                         |               | 40  |     |      |     |     |      | 17  |     | 1   | 42   |     |     |     |     | 15  |      |     |     |
| H                         |               |     |     |      |     |     |      |     |     |     |      |     | 1   |     |     |     |      |     | 2   |
| I                         |               |     |     |      |     |     |      |     | 41  |     |      |     |     |     |     |     |      |     | 1   |
| K                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| L                         |               |     |     |      |     |     | 42   |     |     |     |      | 41  |     |     |     |     |      |     |     |
| M                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| N                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     | 1   |      |     |     |
| P                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     | 2   |     |      |     |     |
| Q                         |               |     |     |      |     |     |      |     |     |     |      |     | 31  |     |     |     |      |     |     |
| R                         |               |     |     |      |     |     |      |     |     |     |      |     | 8   |     |     |     |      |     |     |
| S                         | 42            |     | 1   | 42   |     | 24  |      |     |     | 20  |      |     |     | 20  |     |     |      |     | 1   |
| T                         |               |     | 38  |      |     | 18  |      |     |     | 21  |      |     |     | 17  |     |     |      |     | 3   |
| V                         |               |     |     |      | 1   |     |      | 1   | 1   |     |      | 1   |     | 1   |     |     |      |     |     |
| W                         |               |     |     |      |     |     |      |     |     |     |      |     | 1   |     | 2   |     |      |     |     |
| X                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| Y                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| Z                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| -                         |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| unknown (?)               |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| not sequenced             |               |     |     |      |     |     |      |     |     |     |      |     |     |     |     |     |      |     |     |
| sum of seq <sup>2</sup>   | 42            | 42  | 42  | 42   | 42  | 42  | 42   | 42  | 42  | 42  | 42   | 42  | 42  | 42  | 42  | 42  | 42   | 42  | 42  |
| oomcaa <sup>3</sup>       | 42            | 40  | 38  | 42   | 41  | 24  | 42   | 24  | 41  | 21  | 42   | 41  | 31  | 20  | 24  | 41  | 42   | 38  | 37  |
| mcaa <sup>4</sup>         | S             | G   | T   | S    | A   | S   | L    | A   | I   | T   | G    | L   | Q   | S   | E   | D   | E    | A   | D   |
| rel. oomcaa <sup>5</sup>  | 100%          | 95% | 90% | 100% | 98% | 57% | 100% | 57% | 98% | 50% | 100% | 98% | 74% | 48% | 57% | 98% | 100% | 90% | 88% |
| pos occupied <sup>6</sup> | 1             | 3   | 3   | 1    | 2   | 2   | 1    | 3   | 2   | 3   | 1    | 2   | 5   | 5   | 4   | 2   | 1    | 3   | 5   |

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Table 5A: Analysis of V lambda subgroup 1

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|                           | CDR III |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
|---------------------------|---------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|-----|------|
| amino acid <sup>1</sup>   | 86      | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B   | C   | D    | E    | F    | 96  | 97  | 98   |
| A                         |         |     |      | 22  | 15  |     |     | 1   |     |     |     | 16  |     |      |      |      | 4   | 1   |      |
| B                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| C                         |         |     | 42   |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| D                         |         |     |      |     |     |     | 39  | 17  |     |     | 7   |     |     |      |      |      |     |     |      |
| E                         |         |     |      |     |     |     |     |     |     |     |     | 1   |     |      |      |      | 1   |     |      |
| F                         |         | 2   |      |     |     |     |     |     |     | 1   |     |     |     |      |      |      |     |     | 36   |
| G                         |         |     |      | 14  |     |     |     | 1   |     |     |     | 17  | 1   |      |      |      | 5   | 1   |      |
| H                         |         | 1   |      |     |     |     |     |     |     |     |     |     | 1   |      |      |      |     |     |      |
| I                         |         |     |      |     |     |     |     |     |     |     | 1   |     |     |      |      |      |     | 1   |      |
| K                         |         |     |      |     |     |     |     |     |     |     | 1   |     |     |      |      |      |     |     |      |
| L                         |         |     |      | 1   |     |     |     |     |     | 37  |     |     | 1   |      |      |      |     | 1   |      |
| M                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     | 1   |      |
| N                         |         |     |      |     |     |     | 2   | 2   |     |     | 9   | 1   |     |      |      |      |     |     |      |
| P                         |         |     |      |     |     |     |     |     |     | 1   |     |     |     |      |      |      | 6   |     |      |
| Q                         |         |     |      | 3   |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| R                         |         |     |      |     |     |     |     |     | 5   | 1   | 2   |     |     |      |      |      | 2   |     |      |
| S                         |         |     |      |     | 4   |     |     | 17  | 35  |     | 18  |     | 1   |      |      |      | 1   |     |      |
| T                         |         |     |      |     | 22  |     |     | 1   | 1   |     | 1   |     |     |      |      |      |     |     |      |
| V                         |         |     |      | 1   |     |     |     | 1   |     | 1   |     | 2   |     |      |      |      | 9   | 34  |      |
| W                         |         |     |      |     |     | 38  |     |     |     |     |     |     |     |      |      |      | 7   |     |      |
| X                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| Y                         | 42      | 39  |      |     |     | 3   |     | 1   |     |     |     |     |     |      |      |      | 3   |     |      |
| Z                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| -                         |         |     |      |     |     |     |     |     |     |     | 2   | 4   | 35  | 39   | 38   | 38   | 1   |     |      |
| unknown (?)               |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |
| not sequenced             |         |     |      | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 3   | 3    | 3    | 3    | 3   | 3   | 4    |
| sum of seq <sup>2</sup>   | 42      | 42  | 42   | 41  | 41  | 41  | 41  | 41  | 41  | 41  | 41  | 41  | 39  | 39   | 38   | 38   | 39  | 39  | 36   |
| oomcaa <sup>3</sup>       | 42      | 39  | 42   | 22  | 22  | 38  | 39  | 17  | 35  | 37  | 18  | 17  | 35  | 39   | 38   | 38   | 9   | 34  | 36   |
| mcaa <sup>4</sup>         | Y       | Y   | C    | A   | T   | W   | D   | D   | S   | L   | S   | G   | -   | -    | -    | -    | V   | V   | F    |
| rel. oomcaa <sup>5</sup>  | 100%    | 93% | 100% | 54% | 54% | 93% | 95% | 41% | 85% | 90% | 44% | 41% | 90% | 100% | 100% | 100% | 23% | 87% | 100% |
| pos occupied <sup>6</sup> | 1       | 3   | 1    | 5   | 3   | 2   | 2   | 8   | 3   | 5   | 8   | 6   | 5   | 1    | 1    | 1    | 10  | 6   | 1    |

Table 5A: Analysis of V lambda subgroup 1

|                           | Framework IV |     |      |      |     |     |      |      |     |     |     |     |
|---------------------------|--------------|-----|------|------|-----|-----|------|------|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 99           | 100 | 101  | 102  | 103 | 104 | 105  | 106  | A   | 107 | 108 | sum |
| A                         |              |     |      |      |     |     |      |      |     |     |     | 285 |
| B                         |              |     |      |      |     |     |      |      |     |     |     |     |
| C                         |              |     |      |      |     |     |      |      |     |     |     | 84  |
| D                         |              |     |      |      |     |     |      |      |     |     |     | 224 |
| E                         |              | 1   |      |      |     |     |      |      |     |     |     | 81  |
| F                         |              |     |      |      |     |     |      |      |     |     |     | 87  |
| G                         | 36           | 31  | 36   |      |     |     |      |      |     | 26  |     | 559 |
| H                         |              |     |      |      |     |     |      |      |     |     |     | 25  |
| I                         |              |     |      |      |     |     |      |      |     |     |     | 188 |
| K                         |              |     |      |      | 30  |     |      |      |     |     |     | 141 |
| L                         |              |     |      |      |     | 25  |      |      | 34  |     |     | 344 |
| M                         |              |     |      |      |     |     |      |      |     |     |     | 5   |
| N                         |              |     |      |      | 1   |     |      |      |     |     |     | 176 |
| P                         |              |     |      |      |     |     |      |      |     |     | 1   | 296 |
| Q                         |              |     |      |      | 3   |     |      |      | 1   |     | 18  | 251 |
| R                         |              |     |      |      | 1   |     |      |      |     | 2   |     | 156 |
| S                         |              | 1   |      |      |     |     |      |      |     | 2   |     | 720 |
| T                         |              | 3   |      | 36   | 1   |     | 36   |      |     |     |     | 359 |
| V                         |              |     |      |      |     | 11  |      | 36   | 1   |     |     | 282 |
| W                         |              |     |      |      |     |     |      |      |     | 1   |     | 92  |
| X                         |              |     |      |      |     |     |      |      |     |     |     |     |
| Y                         |              |     |      |      |     |     |      |      |     |     |     | 202 |
| Z                         |              |     |      |      |     |     |      |      |     |     |     | 16  |
| -                         |              |     |      |      |     |     |      |      |     |     |     | 524 |
| unknown (?)               |              |     |      |      |     |     |      |      |     |     |     |     |
| not sequenced             | 4            | 6   | 6    | 6    | 6   | 6   | 6    | 6    | 6   | 6   | 10  | 141 |
| sum of seq <sup>2</sup>   | 36           | 36  | 36   | 36   | 36  | 36  | 36   | 36   | 36  | 36  | 31  | 19  |
| oomcaa <sup>3</sup>       | 36           | 31  | 36   | 36   | 30  | 25  | 36   | 36   | 34  | 26  | 18  |     |
| mcaa <sup>4</sup>         | G            | G   | G    | T    | K   | L   | T    | V    | L   | G   | Q   |     |
| rel. oomcaa <sup>5</sup>  | 100%         | 86% | 100% | 100% | 83% | 69% | 100% | 100% | 94% | 84% | 95% |     |
| pos occupied <sup>6</sup> | 1            | 4   | 1    | 1    | 5   | 2   | 1    | 1    | 3   | 4   | 2   |     |

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Table 5B: Analysis of V lambda subgroup 2

|                           | Framework I |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
|---------------------------|-------------|-----|-----|------|------|-----|------|-----|-----|------|-----|------|-----|-----|-----|-----|-----|------|-----|
| amino acid <sup>1</sup>   | 1           | 2   | 3   | 4    | 5    | 6   | 7    | 8   | 9   | 10   | 11  | 12   | 13  | 14  | 15  | 16  | 17  | 18   | 19  |
| A                         |             |     | 35  |      |      |     |      | 30  |     |      | 6   |      | 1   | 1   |     |     |     |      |     |
| B                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| C                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| D                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     | 1   |     |      |     |
| E                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| F                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| G                         |             |     |     |      |      |     |      |     |     |      |     | 42   |     |     |     | 42  |     |      |     |
| H                         | 2           |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     | 1   |      |     |
| I                         |             |     | 1   |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      | 28  |
| K                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| L                         |             |     |     | 40   |      |     |      |     |     |      |     |      |     |     | 3   |     |     |      | 1   |
| M                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| N                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| P                         |             |     |     |      |      |     | 42   | 6   |     |      |     |      |     |     | 40  |     |     |      |     |
| Q                         | 22          |     | 4   |      |      | 41  |      |     |     |      |     |      |     |     |     |     | 42  |      |     |
| R                         |             |     |     |      |      |     |      | 6   | 1   |      |     |      |     |     |     |     |     |      |     |
| S                         |             | 41  |     |      |      |     |      |     | 40  |      |     | 42   |     | 42  |     |     |     | 43   |     |
| T                         |             |     |     | 42   |      |     |      |     | 1   |      |     |      |     |     |     |     |     |      |     |
| V                         |             | 1   | 2   |      |      |     |      |     |     | 36   |     |      |     |     |     |     |     |      | 14  |
| W                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| X                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| Y                         |             |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| Z                         | 16          |     |     |      |      |     |      |     |     |      |     |      |     |     |     |     |     |      |     |
| -                         |             |     |     |      |      |     |      |     |     | 42   |     |      |     |     |     |     |     |      |     |
| unknown (?)               |             |     |     |      |      | 1   |      |     |     |      |     |      |     |     |     |     |     |      |     |
| not sequenced             | 3           | 1   | 1   | 3    | 1    | 1   | 1    | 1   | 1   | 1    | 1   | 1    |     |     |     |     |     |      |     |
| sum of seq <sup>2</sup>   | 40          | 42  | 42  | 40   | 42   | 42  | 42   | 42  | 42  | 42   | 42  | 42   | 43  | 43  | 43  | 43  | 43  | 43   | 43  |
| oomcaa <sup>3</sup>       | 22          | 41  | 35  | 40   | 42   | 41  | 42   | 30  | 40  | 42   | 36  | 42   | 42  | 42  | 40  | 42  | 42  | 43   | 28  |
| mcaa <sup>4</sup>         | Q           | S   | A   | L    | T    | Q   | P    | A   | S   | -    | V   | S    | G   | S   | P   | G   | Q   | S    | I   |
| rel. oomcaa <sup>5</sup>  | 55%         | 98% | 83% | 100% | 100% | 98% | 100% | 71% | 95% | 100% | 86% | 100% | 98% | 98% | 93% | 98% | 98% | 100% | 65% |
| pos occupied <sup>6</sup> | 3           | 2   | 4   | 1    | 1    | 1   | 1    | 3   | 3   | 1    | 2   | 1    | 2   | 2   | 2   | 2   | 2   | 1    | 3   |

Table 5B: Analysis of V lambda subgroup 2

| amino acid <sup>1</sup>   | CDRI |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
|---------------------------|------|-----|------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|
|                           | 20   | 21  | 22   | 23   | 24  | 25   | 26  | 27  | D   | E   | 28  | 29  | 30  | 31  | A   | 32  | 33  | 34   | 35   |
| A                         |      |     |      |      | 3   |      | 1   |     |     |     |     |     | 1   |     |     | 1   |     |      |      |
| B                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| C                         |      |     |      | 42   |     |      |     |     | 1   |     |     |     |     | 1   |     |     |     |      |      |
| D                         |      |     |      |      |     |      |     |     |     | 39  |     | 1   | 4   |     | 5   |     |     |      |      |
| E                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 1   |     |     |      |      |
| F                         |      | 1   |      |      |     |      |     |     |     |     |     |     | 1   |     |     | 4   |     |      |      |
| G                         |      |     |      |      |     | 43   |     | 1   |     |     |     | 39  | 26  |     |     |     |     |      |      |
| H                         |      |     |      |      |     |      |     | 1   |     |     |     |     |     |     | 1   | 1   |     |      |      |
| I                         |      | 41  |      |      | 1   |      |     |     |     |     | 6   |     |     |     |     |     |     |      |      |
| K                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     | 4   |     |     |      |      |
| L                         |      | 1   |      |      |     |      |     |     |     |     |     |     |     |     |     | 4   |     |      |      |
| M                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| N                         |      |     |      |      |     |      |     | 1   | 3   | 4   |     | 1   | 4   | 3   | 28  |     |     |      |      |
| P                         |      |     |      |      |     |      |     | 1   |     |     |     |     |     |     |     |     |     |      |      |
| Q                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| R                         |      |     |      |      |     |      |     |     | 1   |     |     |     | 2   |     |     |     |     |      |      |
| S                         |      |     | 42   |      | 3   |      | 3   | 35  | 38  |     |     |     | 5   | 1   | 2   | 4   | 1   | 42   |      |
| T                         | 43   |     |      |      | 36  |      | 39  | 3   |     |     |     | 1   |     | 1   |     |     |     |      |      |
| V                         |      |     |      |      |     |      |     |     |     |     | 37  |     |     |     |     |     | 41  |      |      |
| W                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      | 43   |
| X                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| Y                         |      |     |      |      |     |      |     | 1   |     |     |     | 1   |     | 37  |     | 29  |     |      |      |
| Z                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     |     |     |      |      |
| -                         |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     | 1   |     |      |      |
| unknown (?)               |      |     |      |      |     |      |     |     |     |     |     |     |     |     |     | 1   |     |      |      |
| not sequenced             |      |     |      | 1    | 1   |      |     |     |     |     |     |     |     |     |     |     |     | 1    | 1    |
| sum of seq <sup>2</sup>   | 43   | 43  | 42   | 42   | 43  | 43   | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 43  | 42  | 42   | 43   |
| oomcaa <sup>3</sup>       | 43   | 41  | 42   | 42   | 36  | 43   | 39  | 35  | 38  | 39  | 37  | 39  | 26  | 37  | 28  | 29  | 41  | 42   | 43   |
| mcaa <sup>4</sup>         | T    | I   | S    | C    | T   | G    | T   | S   | S   | D   | V   | G   | G   | Y   | N   | Y   | V   | S    | W    |
| rel. oomcaa <sup>5</sup>  | 100% | 95% | 100% | 100% | 84% | 100% | 91% | 81% | 88% | 91% | 86% | 91% | 60% | 86% | 65% | 67% | 98% | 100% | 100% |
| pos occupied <sup>6</sup> | 1    | 3   | 1    | 1    | 4   | 1    | 3   | 7   | 4   | 2   | 2   | 5   | 7   | 5   | 7   | 6   | 2   | 1    | 1    |

Table 5B: Analysis of V lambda subgroup 2

|  | Framework II |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | </ |
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Table 5B: Analysis of V lambda subgroup 2

5b: Analysis of V lambda 5a6g.csp 2

| CDR II                    |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
|---------------------------|------|------|------|------|------|------|------|------|-----|-----|-----|------|-----|------|-----|-----|-----|------|------|--|
| amino acid <sup>1</sup>   | 55   | 56   | A    | B    | C    | D    | E    | 57   | 58  | 59  | 60  | 61   | 62  | 63   | 64  | 65  | 66  | A    | B    |  |
| A                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      | 2   |     |     |      |      |  |
| B                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| C                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     | 1   |     |      |      |  |
| D                         |      |      |      |      |      |      |      |      |     |     | 17  |      |     |      |     |     |     |      |      |  |
| E                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| F                         |      |      |      |      |      |      |      |      |     |     |     |      | 42  |      |     |     |     |      |      |  |
| G                         |      |      |      |      |      |      |      | 43   | 1   |     |     |      |     |      | 41  |     |     |      |      |  |
| H                         |      |      |      |      |      |      |      |      |     |     | 2   |      |     |      |     |     |     |      |      |  |
| I                         |      |      |      |      |      |      |      |      | 3   |     |     |      |     |      |     |     |     |      |      |  |
| K                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     | 42  |      |      |  |
| L                         |      |      |      |      |      |      |      |      |     |     | 1   |      | 1   |      |     |     |     |      |      |  |
| M                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| N                         |      |      |      |      |      |      |      |      |     |     | 19  |      |     |      |     |     |     |      |      |  |
| P                         | 43   |      |      |      |      |      |      |      |     | 15  |     |      |     |      |     |     |     |      |      |  |
| Q                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| R                         |      |      |      |      |      |      |      |      |     |     |     | 43   |     |      |     |     |     | 1    |      |  |
| S                         |      | 43   |      |      |      |      |      |      |     | 28  | 2   |      |     | 43   |     | 42  |     |      |      |  |
| T                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| V                         |      |      |      |      |      |      |      |      | 39  |     |     |      |     |      |     |     |     |      |      |  |
| W                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| X                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| Y                         |      |      |      |      |      |      |      |      |     |     | 2   |      |     |      |     |     |     |      |      |  |
| Z                         |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| -                         |      |      | 43   | 43   | 43   | 43   | 43   |      |     |     |     |      |     |      |     |     |     | 43   | 43   |  |
| unknown (?)               |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| not sequenced             |      |      |      |      |      |      |      |      |     |     |     |      |     |      |     |     |     |      |      |  |
| sum of seq <sup>2</sup>   | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 43  | 43  | 43  | 43   | 43  | 43   | 43  | 43  | 43  | 43   | 43   |  |
| oomcaa <sup>3</sup>       | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 43   | 39  | 28  | 19  | 43   | 42  | 43   | 41  | 42  | 42  | 43   | 43   |  |
| mcaa <sup>4</sup>         | P    | S    | -    | -    | -    | -    | -    | G    | V   | S   | N   | R    | F   | S    | G   | S   | K   | -    | -    |  |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 91% | 65% | 44% | 100% | 98% | 100% | 95% | 98% | 98% | 100% | 100% |  |
| pos occupied <sup>6</sup> | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 3   | 2   | 6   | 1    | 2   | 1    | 2   | 2   | 2   | 1    | 1    |  |

Table 5B: Analysis of V lambda subgroup 2

| amino acid <sup>1</sup>   | Framework III |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
|---------------------------|---------------|-----|-----|-----|------|------|------|------|-----|-----|-----|------|-----|-----|-----|-----|------|------|-----|
|                           | 67            | 68  | 69  | 70  | 71   | 72   | 73   | 74   | 75  | 76  | 77  | 78   | 79  | 80  | 81  | 82  | 83   | 84   | 85  |
| A                         |               | 3   |     | 1   | 43   |      |      |      |     |     |     |      |     | 36  |     |     |      | 43   |     |
| B                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| C                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| D                         |               | 1   | 2   |     |      |      |      |      |     |     |     |      |     |     | 3   | 42  |      |      | 39  |
| E                         |               |     |     |     |      |      |      |      |     |     | 1   |      |     |     | 38  |     | 43   |      |     |
| F                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| G                         |               | 39  |     |     |      |      |      |      |     |     | 42  |      |     |     | 1   |     |      |      |     |
| H                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      | 2   |
| I                         |               |     |     |     |      |      |      |      | 35  |     |     |      |     |     |     |     |      |      |     |
| K                         |               |     | 1   |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| L                         |               |     |     |     |      |      | 43   |      |     |     |     | 43   |     |     |     |     |      |      |     |
| M                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| N                         |               |     | 38  |     |      |      |      |      |     |     |     |      |     |     | 1   | 1   |      |      | 1   |
| P                         |               |     |     |     |      |      |      |      |     |     |     |      |     | 2   |     |     |      |      |     |
| Q                         |               |     |     |     |      |      |      |      |     |     |     |      | 41  |     |     |     |      |      |     |
| R                         |               |     |     |     |      |      |      |      |     |     |     |      | 2   |     |     |     |      |      |     |
| S                         | 42            |     |     | 1   |      | 43   |      |      |     | 42  |     |      |     |     |     |     |      |      |     |
| T                         |               |     | 1   | 41  |      |      |      | 43   |     | 1   |     |      |     | 2   |     |     |      |      |     |
| V                         |               |     |     |     |      |      |      |      | 8   |     |     |      |     | 3   |     |     |      |      |     |
| W                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| X                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| Y                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| Z                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| -                         |               |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| unknown (?)               |               |     | 1   |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      | 1   |
| not sequenced             | 1             |     |     |     |      |      |      |      |     |     |     |      |     |     |     |     |      |      |     |
| sum of seq <sup>2</sup>   | 42            | 43  | 43  | 43  | 43   | 43   | 43   | 43   | 43  | 43  | 43  | 43   | 43  | 43  | 43  | 43  | 43   | 43   | 43  |
| oomcaa <sup>3</sup>       | 42            | 39  | 38  | 41  | 43   | 43   | 43   | 43   | 35  | 42  | 42  | 43   | 41  | 36  | 38  | 42  | 43   | 43   | 39  |
| mcaa <sup>4</sup>         | S             | G   | N   | T   | A    | S    | L    | T    | I   | S   | G   | L    | Q   | A   | E   | D   | E    | A    | D   |
| rel. oomcaa <sup>5</sup>  | 100%          | 91% | 88% | 95% | 100% | 100% | 100% | 100% | 81% | 98% | 98% | 100% | 95% | 84% | 88% | 98% | 100% | 100% | 91% |
| pos occupied <sup>6</sup> | 1             | 3   | 4   | 3   | 1    | 1    | 1    | 1    | 2   | 2   | 2   | 1    | 2   | 4   | 4   | 2   | 1    | 1    | 3   |

Table 5B: Analysis of V lambda subgroup 2

| amino acid <sup>1</sup>   | CDR III |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |      |
|---------------------------|---------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
|                           | 86      | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B   | C   | D    | E    | F    | 96   |
| A                         |         |     |      | 2   | 1   |     | 21  |     | 1   |     |     |     |     |      |      |      | 1    |
| B                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      | 1    |
| C                         |         |     | 43   | 11  |     |     |     |     |     |     |     |     |     |      |      |      |      |
| D                         |         |     |      |     |     |     |     | 3   | 1   | 2   |     |     |     |      |      |      | 1    |
| E                         |         |     |      |     |     |     | 1   | 1   |     |     |     |     |     |      |      |      |      |
| F                         |         | 3   |      |     |     | 3   |     |     |     | 1   |     | 1   |     |      |      |      | 5    |
| G                         |         |     |      |     |     |     | 1   | 21  | 3   | 4   |     |     |     |      |      |      | 1    |
| H                         |         |     |      |     |     | 1   |     |     |     |     |     |     |     |      |      |      |      |
| I                         |         |     |      |     |     |     | 1   | 1   |     | 1   | 2   |     |     |      |      |      | 1    |
| K                         |         |     |      |     |     |     |     |     |     | 3   |     |     |     |      |      |      | 7    |
| L                         |         |     |      |     |     |     |     |     |     |     |     | 1   | 1   |      |      |      | 6    |
| M                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      | 5    |
| N                         |         |     |      |     |     |     |     |     |     | 5   | 7   | 5   |     |      |      |      | 1    |
| P                         |         |     |      |     |     |     |     | 1   |     |     |     |     | 4   |      |      |      |      |
| Q                         |         |     |      |     |     |     |     |     |     | 1   | 2   |     |     |      |      |      |      |
| R                         |         |     |      |     |     |     | 2   |     | 3   |     |     |     | 1   |      |      |      | 5    |
| S                         |         | 1   |      | 30  | 41  |     |     | 12  | 23  | 14  | 9   |     |     |      |      |      | 1    |
| T                         |         |     |      |     |     |     | 16  | 4   | 4   | 3   | 21  |     |     |      |      |      |      |
| V                         |         |     |      |     |     |     | 1   |     |     |     |     |     |     |      |      |      | 11   |
| W                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      | 28   |
| X                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      | 5    |
| Y                         | 43      | 39  |      |     |     | 39  |     |     | 1   | 6   |     |     |     |      |      |      | 4    |
| Z                         |         |     |      |     |     |     |     |     |     |     |     |     |     |      |      |      |      |
| -                         |         |     |      |     |     |     |     |     |     | 1   | 3   | 36  | 42  | 43   | 43   | 43   |      |
| unknown (?)               |         |     |      |     |     |     |     |     | 2   |     |     |     |     |      |      |      |      |
| not sequenced             |         |     |      |     | 1   |     |     |     |     |     | 1   |     |     |      |      |      | 1    |
| sum of seq <sup>2</sup>   | 43      | 43  | 43   | 43  | 42  | 43  | 43  | 43  | 43  | 43  | 42  | 43  | 43  | 43   | 43   | 43   | 42   |
| oomcaa <sup>3</sup>       | 43      | 39  | 43   | 30  | 41  | 39  | 21  | 21  | 23  | 14  | 21  | 36  | 42  | 43   | 43   | 43   | 28   |
| mcaa <sup>4</sup>         | Y       | Y   | C    | S   | S   | Y   | A   | G   | S   | S   | T   | -   | -   | -    | -    | -    | F    |
| rel. oomcaa <sup>5</sup>  | 100%    | 91% | 100% | 70% | 98% | 91% | 49% | 49% | 53% | 33% | 50% | 84% | 98% | 100% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 1       | 3   | 1    | 3   | 2   | 3   | 7   | 7   | 8   | 11  | 6   | 5   | 2   | 1    | 1    | 1    | 1    |

Table 5B: Analysis of V lambda subgroup 2

| amino acid <sup>1</sup>   | Framework IV |     |      |      |     |     |     |      |     |     | sum  |
|---------------------------|--------------|-----|------|------|-----|-----|-----|------|-----|-----|------|
|                           | 99           | 100 | 101  | 102  | 103 | 104 | 105 | 106  | A   | 107 | 108  |
| A                         |              | 1   |      |      |     |     |     |      |     |     | 280  |
| B                         |              |     |      |      |     |     |     |      |     |     |      |
| C                         |              |     |      |      |     |     |     |      |     |     | 99   |
| D                         |              |     |      |      |     |     |     |      |     |     | 188  |
| E                         |              |     |      |      |     |     |     |      |     |     | 107  |
| F                         |              |     |      |      |     |     |     |      |     |     | 113  |
| G                         | 42           | 33  | 42   |      |     |     |     |      |     | 19  | 567  |
| H                         |              |     |      |      |     |     |     |      |     |     | 48   |
| I                         |              |     |      |      |     |     | 1   |      |     |     | 184  |
| K                         |              |     |      |      | 36  |     |     |      |     |     | 189  |
| L                         |              |     |      |      |     | 28  |     |      | 40  |     | 264  |
| M                         |              |     |      |      |     |     |     |      |     |     | 29   |
| N                         |              |     |      |      | 1   |     |     |      |     |     | 146  |
| P                         |              |     |      |      |     |     |     |      |     |     | 238  |
| Q                         |              |     |      |      | 1   |     |     |      |     | 14  | 250  |
| R                         |              | 1   |      |      | 2   |     |     |      |     | 4   | 121  |
| S                         |              |     |      |      |     |     | 1   |      |     | 2   | 831  |
| T                         |              | 7   |      | 41   |     |     | 40  |      |     |     | 398  |
| V                         |              |     |      |      |     | 14  |     | 42   | 1   |     | 327  |
| W                         |              |     |      |      |     |     |     |      |     |     | 48   |
| X                         |              |     |      |      |     |     |     |      |     |     |      |
| Y                         |              |     |      |      | 1   |     |     |      |     |     | 285  |
| Z                         |              |     |      |      |     |     |     |      |     |     | 16   |
| -                         |              |     |      |      |     |     |     |      |     |     | 555  |
| unknown (?)               |              |     |      |      |     |     |     |      |     |     | 8    |
| not sequenced             | 1            | 1   | 1    | 2    | 2   | 1   | 1   | 1    | 2   | 15  | 28   |
| sum of seq <sup>2</sup>   | 42           | 42  | 42   | 41   | 41  | 42  | 42  | 42   | 41  | 25  | 14   |
| oomcaa <sup>3</sup>       | 42           | 33  | 42   | 41   | 36  | 28  | 40  | 42   | 40  | 19  | 14   |
| mcaa <sup>4</sup>         | G            | G   | G    | T    | K   | L   | T   | V    | L   | G   | Q    |
| rel. oomcaa <sup>5</sup>  | 100%         | 79% | 100% | 100% | 88% | 67% | 95% | 100% | 98% | 76% | 100% |
| pos occupied <sup>6</sup> | 1            | 4   | 1    | 1    | 5   | 2   | 3   | 1    | 2   | 3   | 1    |

Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>   | Framework I |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
|---------------------------|-------------|-----|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|------|-----|
|                           | 1           | 2   | 3   | 4   | 5   | 6    | 7   | 8   | 9   | 10   | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18   | 19  |
| A                         |             |     |     |     | 1   |      | 1   | 2   | 7   |      |     |     |     | 20  | 1   |     |     |      | 27  |
| B                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| C                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| D                         |             |     | 5   |     |     |      | 10  |     |     |      |     |     |     |     |     |     |     |      |     |
| E                         |             |     | 20  |     |     |      |     |     |     |      |     |     | 1   |     |     | 1   |     |      |     |
| F                         | 1           | 1   |     |     |     |      |     |     |     |      |     | 1   |     |     | 1   |     |     |      |     |
| G                         |             |     | 1   |     |     |      |     |     |     |      |     |     |     |     |     | 37  |     |      |     |
| H                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| I                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| K                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     | 2   |      |     |
| L                         |             |     |     | 37  |     |      |     |     |     |      | 4   |     | 1   |     | 9   |     |     |      |     |
| M                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| N                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| P                         |             |     |     |     |     |      | 26  | 35  | 1   |      |     |     |     |     | 27  |     |     |      | 1   |
| Q                         | 4           |     | 4   |     |     | 38   |     |     |     |      |     |     |     |     |     |     | 36  |      |     |
| R                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| S                         | 13          | 14  |     |     | 1   |      | 1   |     | 28  |      |     | 37  |     | 18  |     |     |     |      |     |
| T                         |             |     |     |     | 36  |      |     | 1   |     |      |     |     |     |     |     |     |     | 38   |     |
| V                         |             |     | 8   | 1   |     |      |     |     | 2   |      | 34  |     | 36  |     |     |     |     |      | 10  |
| W                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| X                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| Y                         |             | 23  |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| Z                         |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| -                         | 20          |     |     |     |     |      |     |     |     | 38   |     |     |     |     |     |     |     |      |     |
| unknown (?)               |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| not sequenced             |             |     |     |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |     |
| sum of seq <sup>2</sup>   | 38          | 38  | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38  |
| oomcaa <sup>3</sup>       | 20          | 23  | 20  | 37  | 36  | 38   | 26  | 35  | 28  | 38   | 34  | 37  | 36  | 20  | 27  | 37  | 36  | 38   | 27  |
| mcaa <sup>4</sup>         | -           | Y   | E   | L   | T   | Q    | P   | P   | S   | -    | V   | S   | V   | A   | P   | G   | Q   | T    | A   |
| rel. oomcaa <sup>5</sup>  | 53%         | 61% | 53% | 97% | 95% | 100% | 68% | 92% | 74% | 100% | 89% | 97% | 95% | 53% | 71% | 97% | 95% | 100% | 71% |
| pos occupied <sup>6</sup> | 4           | 3   | 5   | 2   | 3   | 1    | 4   | 3   | 4   | 1    | 2   | 2   | 3   | 2   | 4   | 2   | 2   | 1    | 3   |

Table 5C: Analysis of V lambda subgroup 3

|                           | CDRI |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |  |  |
|---------------------------|------|------|-----|------|-----|------|-----|-----|------|------|-----|-----|-----|-----|------|-----|-----|-----|------|--|--|
| amino acid <sup>1</sup>   | 20   | 21   | 22  | 23   | 24  | 25   | 26  | 27  | D    | E    | 28  | 29  | 30  | 31  | A    | 32  | 33  | 34  | 35   |  |  |
| A                         |      |      | 1   |      |     |      |     | 5   |      |      |     |     | 1   | 1   |      |     | 21  | 3   |      |  |  |
| B                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |  |  |
| C                         |      |      |     | 38   |     |      |     |     |      |      |     |     |     |     |      |     |     | 5   |      |  |  |
| D                         |      |      |     |      |     |      | 30  | 1   |      |      |     | 10  |     |     |      | 3   |     | 1   |      |  |  |
| E                         |      |      |     |      |     |      | 2   | 2   |      |      |     | 1   | 3   | 6   |      |     |     |     |      |  |  |
| F                         |      |      |     |      |     |      |     |     |      |      |     |     |     | 1   |      | 2   |     |     |      |  |  |
| G                         |      |      |     |      | 9   | 38   |     | 1   |      |      |     | 23  | 4   |     |      |     |     |     |      |  |  |
| H                         |      |      |     |      |     |      | 1   |     |      |      |     |     |     |     |      | 2   |     | 9   |      |  |  |
| I                         |      | 38   |     |      |     |      |     |     |      |      | 9   |     |     | 1   |      |     |     |     |      |  |  |
| K                         |      |      |     |      |     |      |     | 7   |      |      |     |     | 2   | 13  |      |     |     |     |      |  |  |
| L                         |      |      |     |      |     |      |     |     |      |      | 28  |     |     |     |      |     |     |     |      |  |  |
| M                         | 1    |      |     |      |     |      |     |     |      |      |     |     |     | 1   |      |     |     |     |      |  |  |
| N                         |      |      | 2   |      |     |      | 4   | 9   |      |      | 1   |     | 2   |     |      | 1   |     | 2   |      |  |  |
| P                         |      |      | 1   |      |     |      |     |     |      |      |     | 3   |     |     |      |     |     |     |      |  |  |
| Q                         |      |      |     |      | 10  |      |     |     |      |      |     |     |     | 4   |      |     |     |     |      |  |  |
| R                         | 25   |      |     |      |     |      |     | 2   |      |      |     | 10  | 1   |     |      |     | 1   |     |      |  |  |
| S                         | 9    |      | 1   |      | 19  |      |     | 10  |      |      |     |     | 11  | 2   |      | 8   |     | 14  |      |  |  |
| T                         | 3    |      | 33  |      |     |      |     | 1   |      |      |     | 1   | 4   |     |      |     |     |     |      |  |  |
| V                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      | 1   | 15  |     |      |  |  |
| W                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     | 38   |  |  |
| X                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |  |  |
| Y                         |      |      |     |      |     |      | 1   |     |      |      |     |     |     | 8   |      | 20  | 1   | 4   |      |  |  |
| Z                         |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |  |  |
| -                         |      |      |     |      |     |      |     | 38  | 38   |      |     |     |     |     | 37   |     |     |     |      |  |  |
| unknown (?)               |      |      |     |      |     |      |     |     |      |      |     |     |     |     |      |     |     |     |      |  |  |
| not sequenced             |      |      |     |      |     |      |     |     |      |      |     |     |     |     | 1    | 1   |     |     |      |  |  |
| sum of seq <sup>2</sup>   | 38   | 38   | 38  | 38   | 38  | 38   | 38  | 38  | 38   | 38   | 38  | 38  | 38  | 37  | 37   | 37  | 38  | 38  | 38   |  |  |
| oomcaa <sup>3</sup>       | 25   | 38   | 33  | 38   | 19  | 38   | 30  | 10  | 38   | 38   | 28  | 23  | 11  | 13  | 37   | 20  | 21  | 14  | 38   |  |  |
| mcaa <sup>4</sup>         | R    | I    | T   | C    | S   | G    | D   | S   | -    | -    | L   | G   | S   | K   | -    | Y   | A   | S   | W    |  |  |
| rel. oomcaa <sup>5</sup>  | 66%  | 100% | 87% | 100% | 50% | 100% | 79% | 26% | 100% | 100% | 74% | 61% | 29% | 35% | 100% | 54% | 55% | 37% | 100% |  |  |
| pos occupied <sup>6</sup> | 4    | 1    | 5   | 1    | 3   | 1    | 5   | 9   | 1    | 1    | 3   | 5   | 9   | 9   | 1    | 7   | 4   | 7   | 1    |  |  |

Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>   | Framework II |     |     |     |     |     |     |     |      |     |     |     |     |     | 50  | 51  | 52  | 53  | 54   |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|                           | 36           | 37  | 38  | 39  | 40  | 41  | 42  | 43  | 44   | 45  | 46  | 47  | 48  | 49  |     |     |     |     |      |
| A                         |              |     |     |     |     |     | 23  |     |      |     |     |     |     |     |     | 1   |     | 1   |      |
| B                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| C                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| D                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     | 9   | 22  | 2   | 8   |      |
| E                         |              |     | 1   |     |     |     |     |     |      |     |     |     |     |     | 5   | 3   |     | 3   |      |
| F                         | 3            |     |     |     |     |     |     |     |      |     |     |     |     | 2   |     |     | 1   |     |      |
| G                         |              |     |     |     |     | 36  |     |     |      |     |     |     |     |     | 9   | 2   |     |     |      |
| H                         |              |     |     |     |     |     | 1   |     |      |     |     |     |     | 1   | 3   |     |     | 1   |      |
| I                         |              |     |     |     |     |     |     |     | 1    |     |     | 28  |     |     |     |     | 1   |     |      |
| K                         |              |     |     | 32  |     |     |     |     |      |     |     |     |     |     | 2   | 6   | 1   | 13  |      |
| L                         |              |     | 2   |     |     |     |     |     |      | 6   | 33  | 1   |     |     |     |     |     |     |      |
| M                         |              |     |     |     |     |     |     |     |      |     | 1   |     | 1   |     |     |     |     |     |      |
| N                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 1   | 19  | 9   |      |
| P                         |              |     |     |     | 36  |     | 1   |     | 38   |     |     |     |     |     |     |     |     |     |      |
| Q                         |              | 37  | 35  | 1   |     |     | 36  |     |      |     |     |     |     |     | 9   |     |     | 1   |      |
| R                         |              | 1   |     | 4   |     | 2   |     |     |      |     |     |     |     |     | 1   | 1   |     | 1   | 38   |
| S                         |              |     |     | 1   | 2   |     |     | 14  |      |     |     |     |     |     |     |     | 10  | 1   |      |
| T                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 2   | 4   |     |      |
| V                         |              |     |     |     |     |     |     | 1   |      | 31  | 4   | 37  | 9   |     |     |     |     |     |      |
| W                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| X                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| Y                         | 35           |     |     |     |     |     |     |     |      |     |     |     |     |     | 35  |     |     |     |      |
| Z                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| -                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| unknown (?)               |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| not sequenced             |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |      |
| sum of seq <sup>2</sup>   | 38           | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   |
| oomcaa <sup>1</sup>       | 35           | 37  | 35  | 32  | 36  | 36  | 36  | 23  | 38   | 31  | 33  | 37  | 28  | 35  | 9   | 22  | 19  | 13  | 38   |
| mcaa <sup>1</sup>         | Y            | Q   | Q   | K   | P   | G   | Q   | A   | P    | V   | L   | V   | I   | Y   | D   | D   | N   | K   | R    |
| rel. oomcaa <sup>5</sup>  | 92%          | 97% | 92% | 84% | 95% | 95% | 95% | 61% | 100% | 82% | 87% | 97% | 74% | 92% | 24% | 58% | 50% | 34% | 100% |
| pos occupied <sup>4</sup> | 2            | 2   | 3   | 4   | 2   | 2   | 3   | 3   | 1    | 3   | 3   | 2   | 3   | 3   | 7   | 8   | 7   | 9   | 1    |

Table 5C: Analysis of V lambda subgroup 3

|                           |     | CDR II |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
|---------------------------|-----|--------|------|------|------|------|------|------|------|-----|-----|------|------|------|------|------|-----|------|------|
| amino acid <sup>1</sup>   | 55  | 56     | A    | B    | C    | D    | E    | 57   | 58   | 59  | 60  | 61   | 62   | 63   | 64   | 65   | 66  | A    | B    |
| A                         |     | 1      |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| B                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| C                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| D                         |     |        |      |      |      |      |      |      |      |     | 9   |      |      |      |      |      |     |      |      |
| E                         |     |        |      |      |      |      |      |      |      |     | 27  |      |      |      |      |      |     |      |      |
| F                         |     |        |      |      |      |      |      |      |      |     |     |      | 38   |      |      |      |     |      |      |
| G                         |     |        |      |      |      |      |      | 38   |      |     |     |      |      |      | 38   |      |     |      |      |
| H                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| I                         |     |        |      |      |      |      |      |      | 37   |     |     |      |      |      |      |      |     |      |      |
| K                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| L                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| M                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| N                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      | 21  |      |      |
| P                         | 37  | 1      |      |      |      |      |      |      |      | 36  |     |      |      |      |      |      |     |      |      |
| Q                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| R                         |     |        |      |      |      |      |      |      |      |     |     | 38   |      |      |      |      |     |      |      |
| S                         | 1   | 36     |      |      |      |      |      |      |      | 1   |     |      |      | 38   |      | 38   | 12  |      |      |
| T                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      | 5   |      |      |
| V                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| W                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| X                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| Y                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| Z                         |     |        |      |      |      |      |      |      |      |     |     |      |      |      |      |      |     |      |      |
| -                         |     |        | 38   | 38   | 38   | 38   | 38   |      |      |     |     |      |      |      |      |      |     | 38   | 38   |
| unknown (?)               |     |        |      |      |      |      |      |      |      |     | 1   |      |      |      |      |      |     |      |      |
| not sequenced             |     |        |      |      |      |      |      |      | 1    | 1   | 1   |      |      |      |      |      |     |      |      |
| sum of seq <sup>2</sup>   | 38  | 38     | 38   | 38   | 38   | 38   | 38   | 38   | 37   | 37  | 37  | 38   | 38   | 38   | 38   | 38   | 38  | 38   | 38   |
| oomcaa <sup>3</sup>       | 37  | 36     | 38   | 38   | 38   | 38   | 38   | 38   | 37   | 36  | 27  | 38   | 38   | 38   | 38   | 38   | 21  | 38   | 38   |
| mcaa <sup>4</sup>         | P   | S      | -    | -    | -    | -    | -    | G    | I    | P   | E   | R    | F    | S    | G    | S    | N   | -    | -    |
| rel. oomcaa <sup>5</sup>  | 97% | 95%    | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 97% | 73% | 100% | 100% | 100% | 100% | 100% | 55% | 100% | 100% |
| pos occupied <sup>6</sup> | 2   | 3      | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 2   | 2   | 1    | 1    | 1    | 1    | 1    | 3   | 1    | 1    |



Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
|---------------------------|---------------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|
|                           | 67            | 68  | 69  | 70  | 71  | 72  | 73   | 74  | 75  | 76  | 77  | 78  | 79  | 80  | 81  | 82   | 83   | 84   | 85  |
| A                         |               |     |     | 1   | 36  | 1   |      | 1   |     |     |     | 11  | 1   | 34  |     |      |      | 38   |     |
| B                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| C                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| D                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     | 38   |      |      | 37  |
| E                         |               |     |     |     |     |     |      |     |     |     |     |     | 10  |     | 14  |      | 38   |      | 1   |
| F                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| G                         |               | 37  |     |     |     |     |      |     |     |     | 28  |     |     |     | 10  |      |      |      |     |
| H                         |               |     | 1   |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| I                         |               |     |     |     |     | 1   |      | 1   | 37  | 1   |     |     |     |     | 1   |      |      |      |     |
| K                         |               |     | 1   |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| L                         |               |     |     |     |     |     | 38   |     |     |     |     |     |     |     | 2   |      |      |      |     |
| M                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     | 10  |      |      |      |     |
| N                         |               |     | 28  |     |     |     |      |     |     | 1   |     |     |     |     |     |      |      |      |     |
| P                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| Q                         |               | 1   |     |     |     |     |      |     |     |     |     |     | 25  |     |     |      |      |      |     |
| R                         |               |     |     |     |     |     |      |     |     | 1   | 10  |     | 1   |     |     |      |      |      |     |
| S                         | 37            |     | 2   |     |     | 11  |      |     |     | 23  |     |     |     | 1   |     |      |      |      |     |
| T                         | 1             |     | 6   | 37  |     | 25  |      | 36  |     | 12  |     | 13  |     | 2   |     |      |      |      |     |
| V                         |               |     |     |     | 2   |     |      |     | 1   |     |     | 14  | 1   | 1   | 1   |      |      |      |     |
| W                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| X                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| Y                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| Z                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| -                         |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| unknown (?)               |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| not sequenced             |               |     |     |     |     |     |      |     |     |     |     |     |     |     |     |      |      |      |     |
| sum of seq <sup>1</sup>   | 38            | 38  | 38  | 38  | 38  | 38  | 38   | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38  | 38   | 38   | 38   | 38  |
| oomcaa <sup>1</sup>       | 37            | 37  | 28  | 37  | 36  | 25  | 38   | 36  | 37  | 23  | 28  | 14  | 25  | 34  | 14  | 38   | 38   | 38   | 37  |
| mcaa <sup>1</sup>         | S             | G   | N   | T   | A   | T   | L    | T   | I   | S   | G   | V   | Q   | A   | E   | D    | E    | A    | D   |
| rel. oomcaa <sup>1</sup>  | 97%           | 97% | 74% | 97% | 95% | 66% | 100% | 95% | 97% | 61% | 74% | 37% | 66% | 89% | 37% | 100% | 100% | 100% | 97% |
| pos occupied <sup>1</sup> | 2             | 2   | 5   | 2   | 2   | 4   | 1    | 3   | 2   | 5   | 2   | 3   | 5   | 4   | 6   | 1    | 1    | 1    | 2   |

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Table 5C: Analysis of V lambda subgroup 3

|                           | CDR III |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
|---------------------------|---------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|------|
| amino acid <sup>1</sup>   | 86      | 87  | 88   | 89  | 90  | 91  | 92  | 93  | 94  | 95  | A   | B   | C   | D   | E    | F   | 96  | 97  | 98   |
| A                         |         |     |      |     | 13  | 3   | 2   |     |     | 1   | 2   |     |     |     |      |     | 4   |     |      |
| B                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| C                         |         |     | 38   |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| D                         |         |     |      |     |     |     | 32  | 1   | 1   |     | 6   |     |     |     |      |     |     |     |      |
| E                         |         |     |      | 1   |     |     |     |     |     |     |     | 2   |     |     |      |     | 2   |     |      |
| F                         |         | 2   |      |     |     |     |     | 2   |     |     |     |     |     |     |      |     |     |     | 35   |
| G                         |         |     |      |     |     |     |     |     | 3   | 14  | 3   |     |     | 1   |      |     | 3   | 1   |      |
| H                         |         |     |      |     |     |     |     |     |     |     |     | 12  | 1   |     |      |     |     |     |      |
| I                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     | 4   |      |
| K                         |         |     |      |     |     |     |     |     |     |     | 1   |     |     |     |      |     |     |     |      |
| L                         |         |     |      | 1   |     |     |     | 1   |     | 1   |     | 1   | 1   |     |      |     | 4   | 2   |      |
| M                         |         |     |      |     |     |     |     |     | 1   |     |     |     |     |     |      |     | 1   | 1   |      |
| N                         |         |     |      | 10  |     |     | 2   | 1   | 2   |     | 10  | 1   |     |     |      |     |     |     |      |
| P                         |         |     |      |     |     |     |     |     | 1   |     |     |     | 3   |     |      |     | 1   |     |      |
| Q                         |         |     |      | 25  |     |     |     |     |     | 1   | 1   |     |     |     |      |     |     |     |      |
| R                         |         |     |      |     | 10  |     |     | 1   | 2   |     |     | 2   |     |     |      |     |     |     |      |
| S                         |         |     |      | 1   | 14  | 1   |     | 28  | 26  | 13  |     | 1   |     |     |      | 1   |     |     |      |
| T                         |         |     |      |     |     | 1   |     | 3   |     | 7   | 2   |     |     |     |      |     |     |     |      |
| V                         |         |     |      |     | 11  |     |     |     |     |     |     |     |     |     |      |     | 18  | 28  |      |
| W                         |         |     |      |     |     | 23  |     |     |     |     |     |     |     |     |      |     | 1   |     |      |
| X                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| Y                         | 38      | 36  |      |     |     |     | 1   |     | 1   |     | 1   | 3   | 1   |     |      |     | 3   |     |      |
| Z                         |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| -                         |         |     |      |     |     |     |     |     |     | 10  | 15  | 31  | 36  | 37  | 36   |     |     | 1   |      |
| unknown (?)               |         |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| not sequenced             |         |     |      |     |     |     | 1   | 1   | 1   | 1   | 2   | 1   | 1   | 1   | 1    | 1   | 1   | 1   | 3    |
| sum of seq <sup>2</sup>   | 38      | 38  | 38   | 38  | 38  | 38  | 37  | 37  | 37  | 37  | 36  | 37  | 37  | 37  | 37   | 37  | 37  | 37  | 35   |
| oomcaa <sup>1</sup>       | 38      | 36  | 38   | 25  | 14  | 23  | 32  | 28  | 26  | 14  | 10  | 15  | 31  | 36  | 37   | 36  | 18  | 28  | 35   |
| mcaa <sup>1</sup>         | Y       | Y   | C    | Q   | S   | W   | D   | S   | S   | G   | N   | -   | -   | -   | -    | -   | V   | V   | F    |
| rel. oomcaa <sup>5</sup>  | 100%    | 95% | 100% | 66% | 37% | 61% | 86% | 76% | 70% | 38% | 28% | 41% | 84% | 97% | 100% | 97% | 49% | 76% | 100% |
| pos occupied <sup>6</sup> | 1       | 2   | 1    | 5   | 3   | 5   | 4   | 7   | 8   | 6   | 9   | 8   | 5   | 2   | 1    | 2   | 9   | 6   | 1    |

Table 5C: Analysis of V lambda subgroup 3

| amino acid <sup>1</sup>    | Framework IV |     |      |      |     |     |      |      |     |     |      | sum |
|----------------------------|--------------|-----|------|------|-----|-----|------|------|-----|-----|------|-----|
|                            | 99           | 100 | 101  | 102  | 103 | 104 | 105  | 106  | A   | 107 | 108  |     |
| A                          |              |     |      |      |     |     |      |      |     |     |      | 265 |
| B                          |              |     |      |      |     |     |      |      |     |     |      |     |
| C                          |              |     |      |      |     |     |      |      |     | 1   |      | 82  |
| D                          |              |     |      |      |     |     |      |      |     |     |      | 225 |
| E                          |              |     |      |      | 2   |     |      |      |     |     |      | 145 |
| F                          |              |     |      |      |     |     |      |      |     |     |      | 90  |
| G                          | 35           | 31  | 35   |      |     |     |      |      |     | 24  |      | 461 |
| H                          |              |     |      |      |     |     |      |      |     |     |      | 32  |
| I                          |              |     |      |      |     |     |      |      |     |     |      | 160 |
| K                          |              |     |      |      | 30  |     |      |      |     |     |      | 110 |
| L                          |              |     |      |      |     | 28  |      |      | 33  |     |      | 233 |
| M                          |              |     |      |      |     |     |      |      |     |     |      | 17  |
| N                          |              |     |      |      |     |     |      |      |     |     |      | 126 |
| P                          |              |     |      |      |     |     |      |      | 1   |     |      | 249 |
| Q                          |              |     |      |      |     |     |      |      |     |     | 7    | 275 |
| R                          |              |     |      |      | 2   |     |      |      |     |     |      | 154 |
| S                          |              |     |      |      |     |     |      |      |     | 2   |      | 501 |
| T                          |              | 4   |      | 35   |     |     | 35   |      |     |     |      | 347 |
| V                          |              |     |      |      |     | 7   |      | 35   |     |     |      | 308 |
| W                          |              |     |      |      |     |     |      |      |     |     |      | 62  |
| X                          |              |     |      |      |     |     |      |      |     |     |      |     |
| Y                          |              |     |      |      |     |     |      |      |     |     |      | 211 |
| Z                          |              |     |      |      |     |     |      |      |     |     |      |     |
| -                          |              |     |      |      |     |     |      |      |     |     |      | 603 |
| unknown (?)                |              |     |      |      |     |     |      |      |     |     |      | 1   |
| not sequenced <sup>2</sup> | 3            | 3   | 3    | 3    | 4   | 3   | 3    | 3    | 3   | 4   | 11   | 89  |
| sum of seq <sup>3</sup>    | 35           | 35  | 35   | 35   | 34  | 35  | 35   | 35   | 34  | 27  | 7    |     |
| oomcaa <sup>3</sup>        | 35           | 31  | 35   | 35   | 30  | 28  | 35   | 35   | 33  | 24  | 7    |     |
| mcaa <sup>4</sup>          | G            | G   | G    | T    | K   | L   | T    | V    | L   | G   | Q    |     |
| rel. oomcaa <sup>5</sup>   | 100%         | 89% | 100% | 100% | 88% | 80% | 100% | 100% | 97% | 89% | 100% |     |
| pos occupied <sup>6</sup>  | 1            | 2   | 1    | 1    | 3   | 2   | 1    | 1    | 2   | 3   | 1    |     |

Table 6A: Analysis of V heavy chain subgroup 1A

| amino acid <sup>1</sup>   | Framework I |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
|---------------------------|-------------|-----|-----|-----|-----|-----|------|-----|-----|------|-----|-----|------|-----|------|-----|-----|------|-----|------|
|                           | 1           | 2   | 3   | 4   | 5   | 6   | 7    | 8   | 9   | 10   | 11  | 12  | 13   | 14  | 15   | 16  | 17  | 18   | 19  | 20   |
| A                         |             |     |     |     | 1   | 14  |      |     | 60  |      |     |     |      |     |      | 24  | 1   |      |     |      |
| B                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| C                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| D                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| E                         | 1           |     |     |     | 2   | 1   |      | 2   |     | 64   |     |     |      |     |      |     |     |      |     |      |
| F                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| G                         |             |     |     |     |     |     |      | 58  | 1   |      |     |     |      |     | 64   |     |     |      |     |      |
| H                         |             |     | 2   |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| I                         |             | 2   |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| K                         |             | 2   |     |     |     |     |      |     |     |      |     | 57  | 64   |     |      |     |     |      | 60  |      |
| L                         |             |     | 2   | 59  |     |     |      |     |     |      | 3   |     |      |     |      |     |     |      |     |      |
| M                         |             | 1   |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| N                         |             |     |     |     |     |     |      |     |     |      |     | 6   |      |     |      |     |     |      |     |      |
| P                         |             |     |     |     |     |     |      |     |     |      |     |     |      | 63  |      |     |     |      |     |      |
| Q                         | 53          |     | 56  |     | 2   | 45  |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| R                         |             |     |     |     |     |     |      |     |     |      |     | 1   |      |     |      |     |     |      | 3   |      |
| S                         |             |     |     |     |     |     | 60   |     | 3   |      |     |     |      | 1   |      | 40  | 63  |      |     |      |
| T                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      | 1   |      |
| V                         | 2           | 55  |     | 1   | 55  |     |      |     |     | 61   |     |     |      |     |      |     |     | 64   |     | 64   |
| W                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| X                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| Y                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| Z                         | 3           |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| -                         |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| unknown (?)               |             |     |     |     |     |     |      |     |     |      |     |     |      |     |      |     |     |      |     |      |
| not sequenced             | 11          | 10  | 10  | 10  | 10  | 10  | 10   | 10  | 6   | 6    | 6   | 6   | 6    | 6   | 6    | 6   | 6   | 6    | 6   | 6    |
| sum of seq <sup>2</sup>   | 59          | 60  | 60  | 60  | 60  | 60  | 60   | 60  | 64  | 64   | 64  | 64  | 64   | 64  | 64   | 64  | 64  | 64   | 64  | 64   |
| oomcaa <sup>3</sup>       | 53          | 55  | 56  | 59  | 55  | 45  | 60   | 58  | 60  | 64   | 61  | 57  | 64   | 63  | 64   | 40  | 63  | 64   | 60  | 64   |
| mcaa <sup>4</sup>         | Q           | V   | Q   | L   | V   | Q   | S    | G   | A   | E    | V   | K   | K    | P   | G    | S   | S   | V    | K   | V    |
| rel. oomcaa <sup>5</sup>  | 90%         | 92% | 93% | 98% | 92% | 75% | 100% | 97% | 94% | 100% | 95% | 89% | 100% | 98% | 100% | 63% | 98% | 100% | 94% | 100% |
| pos occupied <sup>6</sup> | 4           | 4   | 3   | 2   | 4   | 3   | 1    | 2   | 3   | 1    | 2   | 3   | 1    | 2   | 1    | 2   | 2   | 1    | 3   | 1    |

Table 6A: Analysis of V heavy chain subgroup 1A

| amino acid <sup>1</sup>   |     |     |     |     |      |      |     |     |     |     | CDRI |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
|---------------------------|-----|-----|-----|-----|------|------|-----|-----|-----|-----|------|------|------|-----|-----|-----|-----|------|-----|------|----|----|----|----|----|----|----|----|----|----|----|----|----|
|                           | 21  | 22  | 23  | 24  | 25   | 26   | 27  | 28  | 29  | 30  | 31   | A    | B    | 32  | 33  | 34  | 35  | 36   | 37  | 38   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| A                         |     |     |     | 62  |      |      |     | 1   |     |     |      |      |      |     | 41  |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| B                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| C                         |     | 63  |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| D                         |     |     |     |     |      |      | 1   |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| E                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| F                         |     |     |     |     |      |      |     |     | 69  |     |      |      |      |     | 3   |     | 3   |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| G                         |     |     |     | 1   |      | 69   | 41  |     | 1   |     |      |      |      |     |     | 23  |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| H                         |     |     |     |     |      |      |     |     |     | 1   |      |      |      |     | 1   |     |     | 1    |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| I                         |     |     |     |     |      |      |     | 1   |     |     |      |      |      |     |     |     | 61  | 1    |     | 1    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| K                         |     |     | 63  |     |      |      |     |     |     |     | 1    | 1    |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| L                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     | 1   | 2   |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| M                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     | 4   |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| N                         |     |     |     |     |      |      |     |     |     |     | 2    | 5    |      |     |     |     |     | 4    |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| P                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     | 1   |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Q                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| R                         |     | 1   | 1   |     |      |      |     |     |     |     | 1    | 1    |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    | 70 |    |
| S                         | 63  |     |     |     | 68   |      |     | 1   |     |     | 40   | 60   |      |     | 2   |     |     | 60   |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| T                         | 1   |     |     | 2   |      |      |     | 68  |     |     | 25   | 3    |      |     |     | 3   |     | 4    |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| V                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     | 1   |     |      |     |      |    |    |    |    |    |    |    |    |    | 69 |    |    |    |
| W                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     | 70   |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| X                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y                         |     |     |     |     |      |      |     | 27  |     |     |      |      |      |     |     | 64  |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Z                         |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| -                         |     |     |     |     |      |      |     |     |     |     |      | 70   | 70   |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| unknown (?)               |     |     |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| not sequenced             | 6   | 6   | 6   | 5   | 2    | 1    |     |     |     |     |      |      |      |     |     |     |     |      |     |      |    |    |    |    |    |    |    |    |    |    |    |    |    |
| sum of seq <sup>2</sup>   | 64  | 64  | 64  | 65  | 68   | 69   | 70  | 70  | 70  | 70  | 70   | 70   | 70   | 70  | 70  | 70  | 70  | 70   | 70  | 70   | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| oomcaa <sup>3</sup>       | 63  | 63  | 63  | 62  | 68   | 69   | 41  | 68  | 69  | 40  | 60   | 70   | 70   | 64  | 41  | 61  | 60  | 70   | 69  | 70   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| mcaa <sup>4</sup>         | S   | C   | K   | A   | S    | G    | G   | T   | F   | S   | S    | -    | -    | Y   | A   | I   | S   | W    | V   | R    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| rel. oomcaa <sup>5</sup>  | 98% | 98% | 98% | 95% | 100% | 100% | 59% | 97% | 99% | 57% | 86%  | 100% | 100% | 91% | 59% | 87% | 86% | 100% | 99% | 100% |    |    |    |    |    |    |    |    |    |    |    |    |    |
| pos occupied <sup>6</sup> | 2   | 2   | 2   | 3   | 1    | 1    | 4   | 3   | 2   | 6   | 5    | 1    | 1    | 4   | 6   | 4   | 5   | 1    | 2   | 1    |    |    |    |    |    |    |    |    |    |    |    |    |    |

Table 6A: Analysis of V heavy chain subgroup 1A

|                           |     | Framework II |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
|---------------------------|-----|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|--|--|--|--|--|
| amino acid <sup>1</sup>   | 39  | 40           | 41  | 42  | 43  | 44  | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52  | A   | B    | C    | 53  | 54  | 55  |  |  |  |  |  |
| A                         |     | 70           |     |     |     |     |     |     |     |     | 1   |     |     |     | 5   |      |      |     |     |     |  |  |  |  |  |
| B                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| C                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| D                         |     |              |     |     |     |     |     | 1   |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| E                         |     |              |     |     |     |     |     | 69  |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| F                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| G                         |     |              | 1   | 68  |     | 69  |     |     | 1   |     | 69  | 39  |     |     | 1   |      |      | 3   | 39  |     |  |  |  |  |  |
| H                         |     |              | 1   |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     | 68  |  |  |  |  |  |
| I                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| K                         |     |              |     |     |     |     |     |     |     |     |     |     | 65  | 38  |     |      |      | 34  |     |     |  |  |  |  |  |
| L                         |     |              |     | 1   |     | 68  |     |     | 1   |     | 1   |     |     |     |     |      |      | 2   | 4   |     |  |  |  |  |  |
| M                         |     |              |     |     |     |     |     |     | 67  |     |     |     |     | 2   |     |      |      | 4   |     |     |  |  |  |  |  |
| N                         |     |              |     |     |     |     |     |     |     |     |     |     |     | 4   |     |      |      | 3   | 22  |     |  |  |  |  |  |
| P                         |     |              | 68  |     |     |     | 1   |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| Q                         | 69  |              |     | 69  |     |     |     |     |     |     |     |     |     | 44  |     |      |      |     |     |     |  |  |  |  |  |
| R                         | 1   |              |     | 1   |     | 1   |     |     |     |     |     | 4   |     |     |     |      |      | 1   | 1   | 1   |  |  |  |  |  |
| S                         |     |              |     |     | 1   |     |     |     | 1   | 1   |     |     |     | 22  |     |      |      | 1   |     |     |  |  |  |  |  |
| T                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     | 1   | 1   |  |  |  |  |  |
| V                         |     |              |     |     |     |     |     |     |     |     |     |     | 1   | 2   | 4   |      |      | 1   | 3   |     |  |  |  |  |  |
| W                         |     |              |     |     |     | 1   |     | 67  |     |     |     | 26  |     | 2   | 2   | 16   |      | 1   |     |     |  |  |  |  |  |
| X                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| Y                         |     |              |     |     |     |     |     |     | 1   |     |     |     |     |     |     |      |      | 20  |     |     |  |  |  |  |  |
| Z                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| -                         |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| unknown (?)               |     |              |     |     |     |     |     |     |     |     |     |     |     |     | 70  | 70   |      |     |     |     |  |  |  |  |  |
| not sequenced             |     |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |  |
| sum of seq <sup>2</sup>   | 70  | 70           | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70   | 70   | 70  | 70  | 70  |  |  |  |  |  |
| oomcaa <sup>3</sup>       | 69  | 70           | 68  | 68  | 69  | 69  | 68  | 69  | 67  | 67  | 69  | 39  | 65  | 38  | 44  | 70   | 70   | 34  | 39  | 68  |  |  |  |  |  |
| mcaa <sup>4</sup>         | Q   | A            | P   | G   | Q   | G   | L   | E   | W   | M   | G   | G   | I   | I   | P   | -    | -    | I   | F   | G   |  |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 99% | 100%         | 97% | 97% | 99% | 99% | 97% | 99% | 96% | 96% | 99% | 56% | 93% | 54% | 63% | 100% | 100% | 49% | 56% | 97% |  |  |  |  |  |
| pos occupied <sup>6</sup> | 2   | 1            | 3   | 3   | 2   | 2   | 3   | 2   | 4   | 4   | 2   | 4   | 4   | 6   | 5   | 1    | 1    | 10  | 6   | 3   |  |  |  |  |  |

Table 6A: Analysis of V heavy chain subgroup 1A

| amino acid <sup>1</sup>   | CDR II |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
|---------------------------|--------|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|------|-----|
|                           | 56     | 57  | 58  | 59  | 60  | 61   | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72   | 73  | 74   | 75  |
| A                         | 1      | 34  |     |     | 69  |      |     |     |     |     |     |     |     |     |     | 43  |      |     |      |     |
| B                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| C                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| D                         | 15     |     | 1   |     |     |      |     |     |     | 2   |     |     |     |     |     |     | 70   |     |      |     |
| E                         |        |     |     |     |     |      |     |     | 1   |     |     |     |     |     |     |     |      | 33  |      |     |
| F                         |        |     |     | 1   |     |      | 48  |     |     |     |     | 3   |     | 4   |     |     |      |     |      |     |
| G                         | 1      |     |     |     |     |      | 3   |     |     | 67  |     |     |     |     |     |     |      |     |      |     |
| H                         |        |     | 1   |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| I                         | 4      |     |     |     |     |      |     |     |     |     |     |     | 1   | 44  |     |     |      | 1   |      |     |
| K                         | 1      |     | 2   | 1   |     |      | 47  |     | 1   |     | 1   |     |     |     |     |     |      | 8   |      |     |
| L                         | 1      | 1   |     |     |     |      |     | 22  |     |     |     | 2   |     | 1   |     | 3   |      |     |      |     |
| M                         |        |     |     |     |     |      |     |     |     |     |     |     |     | 21  |     |     |      |     |      |     |
| N                         | 9      |     | 59  |     |     |      | 18  |     |     |     |     |     |     |     |     |     |      |     |      |     |
| P                         | 1      | 7   |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| Q                         | 1      | 1   |     |     |     | 70   |     |     | 64  |     |     |     |     |     |     |     |      |     |      |     |
| R                         | 2      |     |     |     |     |      | 2   |     | 1   |     | 69  |     |     |     |     |     |      | 1   |      |     |
| S                         |        | 1   | 2   |     | 1   |      |     |     |     |     |     |     |     |     |     | 5   |      |     | 70   |     |
| T                         | 34     | 26  | 4   |     |     |      |     |     | 3   |     |     |     | 66  |     | 65  | 24  |      | 27  |      | 67  |
| V                         |        |     |     |     |     |      |     |     |     | 1   |     | 65  | 3   |     |     |     |      |     |      | 3   |
| W                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| X                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| Y                         |        |     | 1   | 68  |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| Z                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| -                         |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| unknown (?)               |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| not sequenced             |        |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |     |
| sum of seq <sup>2</sup>   | 70     | 70  | 70  | 70  | 70  | 70   | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70   | 70  | 70   | 70  |
| oomcaa <sup>3</sup>       | 34     | 34  | 59  | 68  | 69  | 70   | 47  | 48  | 64  | 67  | 69  | 65  | 66  | 44  | 65  | 43  | 70   | 33  | 70   | 67  |
| mcaa <sup>4</sup>         | T      | A   | N   | Y   | A   | Q    | K   | F   | Q   | G   | R   | V   | T   | I   | T   | A   | D    | E   | S    | T   |
| rel. oomcaa <sup>5</sup>  | 49%    | 49% | 84% | 97% | 99% | 100% | 67% | 69% | 91% | 96% | 99% | 93% | 94% | 63% | 93% | 61% | 100% | 47% | 100% | 96% |
| pos occupied <sup>6</sup> | 11     | 6   | 7   | 3   | 2   | 1    | 4   | 2   | 5   | 3   | 2   | 3   | 3   | 4   | 2   | 3   | 1    | 5   | 1    | 2   |

Table 6A: Analysis of V heavy chain subgroup 1A

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|------|-----|------|-----|-----|-----|------|
|                           | 76            | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C    | 83  | 84  | 85  | 86   | 87  | 88   | 89  | 90  | 91  | 92   |
| A                         |               |     | 64  |     |     | 1   |     |     |     |      |     | 3   |     |      | 1   | 70   |     |     |     |      |
| B                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| C                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     | 70   |
| D                         |               |     |     |     |     | 2   |     |     |     |      |     |     | 26  | 70   |     |      |     |     |     |      |
| E                         |               |     |     |     | 64  |     |     |     |     |      |     |     | 44  |      |     |      |     |     |     |      |
| F                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| G                         |               |     |     |     |     |     |     |     | 1   |      |     |     |     |      |     |      | 1   | 1   | 2   |      |
| H                         |               |     |     | 1   |     |     |     | 1   |     |      |     |     |     |      |     |      |     |     |     |      |
| I                         |               | 1   |     |     |     |     | 3   | 1   | 1   |      |     |     |     |      |     |      |     |     |     |      |
| K                         |               |     |     |     |     |     |     |     |     |      |     | 3   |     |      |     |      |     |     |     |      |
| L                         |               |     |     |     | 3   | 63  |     |     | 70  |      |     |     |     |      |     |      |     |     |     |      |
| M                         |               |     |     |     | 67  |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| N                         | 4             |     |     |     |     |     |     | 1   | 16  |      |     |     |     |      | 1   |      | 1   |     |     |      |
| P                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| Q                         |               |     |     | 1   |     | 3   |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| R                         | 3             |     |     |     |     |     | 23  | 1   |     | 62   |     |     |     |      |     |      |     |     |     |      |
| S                         | 62            |     | 1   |     |     |     | 41  | 49  |     |      | 67  |     |     |      | 1   |      |     |     |     |      |
| T                         | 1             | 69  | 2   |     |     |     | 3   | 2   |     | 4    |     |     |     | 67   |     |      |     |     |     |      |
| V                         |               |     | 3   |     |     |     | 4   |     |     | 1    |     |     |     |      |     |      |     |     |     |      |
| W                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      | 64  |     |     |      |
| X                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| Y                         |               |     | 68  |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| Z                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     | 69  | 68  |      |
| -                         |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| unknown (?)               |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| not sequenced             |               |     |     |     |     |     |     |     |     |      |     |     |     |      |     |      |     |     |     |      |
| sum of seq <sup>2</sup>   | 70            | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70  | 70   | 70  | 70  | 70  | 70   | 70  | 70   | 70  | 70  | 70  | 70   |
| oomcaa <sup>3</sup>       | 62            | 69  | 64  | 68  | 67  | 64  | 63  | 41  | 49  | 70   | 62  | 67  | 44  | 70   | 67  | 70   | 64  | 69  | 68  | 70   |
| mcaa <sup>4</sup>         | S             | T   | A   | Y   | M   | E   | L   | S   | S   | L    | R   | S   | E   | D    | T   | A    | V   | Y   | Y   | C    |
| rel. oomcaa <sup>5</sup>  | 89%           | 99% | 91% | 97% | 96% | 91% | 90% | 59% | 70% | 100% | 89% | 96% | 63% | 100% | 96% | 100% | 91% | 99% | 97% | 100% |
| pos occupied <sup>6</sup> | 4             | 2   | 4   | 3   | 2   | 4   | 3   | 6   | 6   | 1    | 4   | 2   | 2   | 1    | 4   | 1    | 5   | 2   | 2   | 1    |

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Table 6A: Analysis of V heavy chain subgroup 1A

| CDR III                   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 93  | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   | 101 |
| A                         | 66  | 2   | 16  |     | 1   | 1   | 1   | 4   | 1   | 2   | 2   | 1   | 1   |     | 1   | 1   | 1   | 2   |     | 1   |
| B                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |     |     |     |     | 1   | 1   | 16  | 2   |     | 1   | 1   | 7   | 2   | 1   |     |     |     |     |     |     |
| D                         |     |     | 16  | 5   | 3   |     | 3   | 5   | 4   | 3   | 4   |     |     | 1   | 1   | 14  |     |     |     | 59  |
| E                         |     |     | 9   |     |     |     | 2   |     |     | 1   |     |     | 1   |     |     | 1   |     |     |     |     |
| F                         |     |     |     |     | 1   | 3   |     | 2   |     | 3   | 1   | 2   |     | 2   | 1   |     |     |     | 28  | 2   |
| G                         |     | 2   | 14  | 13  | 20  | 10  | 14  | 5   | 20  | 15  | 16  | 3   | 3   | 4   | 15  | 1   | 1   | 7   |     |     |
| H                         |     |     |     |     |     |     |     |     |     | 1   | 1   | 1   |     | 1   |     |     |     |     |     |     |
| I                         |     |     |     | 2   | 5   | 2   | 2   |     | 2   | 2   | 1   | 1   |     |     | 1   |     |     |     |     |     |
| K                         |     | 5   |     |     | 2   | 1   |     |     | 1   |     |     |     |     |     |     |     |     |     |     |     |
| L                         |     | 1   | 4   | 4   | 2   | 5   | 2   | 1   | 1   |     | 4   | 2   |     | 1   |     |     | 1   |     | 1   |     |
| M                         |     |     | 1   |     | 2   |     | 1   |     | 1   |     |     | 1   | 1   |     |     |     |     |     | 10  |     |
| N                         |     |     |     | 2   | 2   | 1   | 2   | 1   | 2   | 2   | 2   | 2   |     |     | 1   | 1   | 4   |     |     |     |
| P                         |     |     |     | 20  | 3   |     | 1   | 3   | 2   | 2   | 2   | 4   | 2   | 1   | 4   | 1   |     | 1   |     | 1   |
| Q                         |     |     |     | 1   |     |     | 1   |     | 1   | 1   | 1   |     |     |     |     |     |     |     |     |     |
| R                         |     | 55  | 1   | 5   | 7   | 8   | 1   | 4   |     | 2   |     | 1   |     | 16  |     |     |     |     |     |     |
| S                         |     | 1   | 1   | 5   | 5   | 5   | 5   | 21  | 5   | 11  | 8   | 4   | 3   |     | 2   | 1   |     | 2   |     | 1   |
| T                         | 1   | 3   | 3   | 5   | 4   | 1   | 3   | 4   | 2   | 5   | 2   |     | 1   |     |     | 1   | 1   |     |     |     |
| V                         | 3   |     | 3   | 2   | 4   | 3   | 3   | 3   | 4   | 2   | 2   | 2   | 1   | 2   | 1   |     |     |     |     |     |
| W                         |     |     |     | 1   | 1   | 3   | 1   | 1   |     |     | 2   |     | 3   |     |     |     | 1   | 5   | 1   |     |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |     | 1   |     | 2   | 3   | 20  | 5   | 4   | 9   | 1   | 2   | 11  | 20  | 10  | 6   | 9   | 10  | 7   | 1   |     |
| Z                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |     |     |     | 1   | 2   | 2   | 3   | 6   | 11  | 11  | 14  | 23  | 26  | 26  | 31  | 34  | 46  | 39  | 21  | 1   |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     | 1   |     | 1   | 1   |     | 2   | 3   |     |
| not sequenced             |     |     | 2   | 2   | 2   | 4   | 4   | 4   | 4   | 5   | 5   | 5   | 5   | 5   | 5   | 5   | 5   | 5   | 5   | 5   |
| sum of seq <sup>2</sup>   | 70  | 70  | 68  | 68  | 68  | 66  | 66  | 66  | 66  | 65  | 65  | 65  | 65  | 65  | 65  | 65  | 65  | 65  | 65  | 65  |
| oomcaa <sup>3</sup>       | 66  | 55  | 16  | 20  | 20  | 20  | 16  | 21  | 20  | 15  | 16  | 23  | 26  | 26  | 31  | 34  | 46  | 39  | 28  | 59  |
| mcaa <sup>4</sup>         | A   | R   | A   | P   | G   | Y   | C   | S   | G   | -   | -   | -   | -   | -   | -   | -   | -   | -   | F   | D   |
| rel. oomcaa <sup>5</sup>  | 94% | 79% | 24% | 29% | 29% | 30% | 24% | 32% | 30% | 23% | 25% | 35% | 40% | 40% | 48% | 52% | 71% | 60% | 43% | 91% |
| pos occupied <sup>6</sup> | 3   | 8   | 10  | 14  | 18  | 15  | 18  | 15  | 15  | 17  | 17  | 15  | 12  | 11  | 11  | 10  | 8   | 7   | 6   | 6   |

Table 6A: Analysis of V heavy chain subgroup 1A

| Framework IV              |     |     |     |     |      |     |     |     |     |      |     |     |     |
|---------------------------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|
| amino acid <sup>1</sup>   | 102 | 103 | 104 | 105 | 106  | 107 | 108 | 109 | 110 | 111  | 112 | 113 | sum |
| A                         |     |     |     |     |      |     |     |     |     |      |     |     | 670 |
| B                         |     |     |     |     |      |     |     |     |     |      |     |     |     |
| C                         |     |     |     |     |      |     |     |     |     |      |     |     | 165 |
| D                         |     | 1   | 1   |     |      |     |     |     |     |      |     |     | 308 |
| E                         | 1   | 1   |     |     |      |     |     |     |     |      |     |     | 297 |
| F                         | 2   |     |     |     |      |     |     |     |     |      |     |     | 226 |
| G                         |     |     | 58  | 59  | 1    | 1   |     |     |     |      |     |     | 928 |
| H                         |     |     |     | 1   |      |     |     |     |     |      |     |     | 14  |
| I                         | 3   |     |     |     |      |     |     |     | 4   |      |     |     | 286 |
| K                         |     |     |     | 3   |      | 1   |     |     |     |      |     |     | 325 |
| L                         | 3   |     |     | 1   |      |     | 40  | 1   |     |      |     |     | 386 |
| M                         | 1   |     |     |     |      |     | 3   |     |     |      |     |     | 189 |
| N                         |     |     |     | 1   |      |     |     |     |     |      |     |     | 176 |
| P                         | 5   |     |     |     |      |     |     |     |     |      |     | 1   | 238 |
| Q                         |     |     |     | 52  |      |     |     |     |     |      |     |     | 494 |
| R                         |     |     |     | 1   |      |     |     |     |     |      |     |     | 351 |
| S                         |     |     |     |     |      |     |     |     |     |      | 53  | 51  | 972 |
| T                         |     |     |     |     |      | 54  | 11  | 1   | 51  |      | 1   |     | 736 |
| V                         | 15  |     | 1   |     |      |     | 1   | 54  |     | 54   |     | 1   | 699 |
| W                         |     | 59  |     | 1   |      |     |     |     |     |      |     |     | 243 |
| X                         |     |     |     |     |      |     |     |     |     |      |     |     |     |
| Y                         | 34  |     | 1   |     |      |     |     |     |     |      |     |     | 542 |
| Z                         |     |     |     |     |      |     |     |     |     |      |     |     | 3   |
| -                         | 1   |     |     |     |      |     |     |     |     |      |     |     | 578 |
| unknown (?)               |     |     |     |     |      |     |     |     |     |      |     |     | 8   |
| not sequenced             | 5   | 9   | 9   | 10  | 11   | 14  | 14  | 14  | 15  | 16   | 16  | 17  | 406 |
| sum of seq <sup>2</sup>   | 65  | 61  | 61  | 60  | 59   | 56  | 56  | 56  | 55  | 54   | 54  | 53  |     |
| oomcaa <sup>3</sup>       | 34  | 59  | 58  | 52  | 59   | 54  | 40  | 54  | 51  | 54   | 53  | 51  |     |
| mcaa <sup>4</sup>         | Y   | W   | G   | Q   | G    | T   | L   | V   | T   | V    | S   | S   |     |
| rel. oomcaa <sup>5</sup>  | 52% | 97% | 95% | 87% | 100% | 96% | 71% | 96% | 93% | 100% | 98% | 96% |     |
| pos occupied <sup>6</sup> | 9   | 3   | 4   | 7   | 1    | 3   | 5   | 3   | 2   | 1    | 2   | 3   |     |

Table 68: Analysis of V heavy chain subgroup 1B

| Framework I                |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
|----------------------------|-----|-----|-----|-----|-----|-----|------|------|-----|------|------|-----|-----|-----|------|-----|-----|------|-----|-----|
| amino acid <sup>1</sup>    | 1   | 2   | 3   | 4   | 5   | 6   | 7    | 8    | 9   | 10   | 11   | 12  | 13  | 14  | 15   | 16  | 17  | 18   | 19  | 20  |
| A                          |     |     |     |     |     |     |      |      | 32  |      |      |     |     |     |      | 34  |     |      |     |     |
| B                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| C                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| D                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| E                          |     | 1   |     |     | 5   | 1   |      |      | 35  |      |      |     |     |     |      |     |     |      |     |     |
| F                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| G                          |     |     |     |     |     |     |      | 27   |     |      |      |     |     |     | 35   |     |     |      |     |     |
| H                          |     |     | 1   |     |     |     |      |      |     |      |      |     |     | 1   |      |     |     |      |     |     |
| I                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      | 1   |     |
| K                          |     | 3   | 1   |     |     |     |      |      |     |      |      | 34  | 33  |     |      |     |     | 33   |     |     |
| L                          |     |     | 3   | 26  | 1   |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| M                          |     |     |     | 1   | 1   |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| N                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| P                          |     |     |     |     |     |     |      |      | 1   |      |      |     | 33  |     |      |     | 1   |      |     |     |
| Q                          | 21  | 20  |     |     | 26  |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| R                          | 1   |     |     |     |     |     |      |      |     |      |      | 1   | 2   |     |      |     |     |      |     |     |
| S                          |     |     |     |     |     |     | 27   |      |     |      |      |     |     |     |      |     | 1   | 34   |     |     |
| T                          |     |     |     |     |     |     |      |      | 1   |      |      |     |     | 1   |      |     |     |      | 2   |     |
| V                          | 3   | 21  |     |     | 20  |     |      |      |     | 35   |      |     |     |     |      |     |     | 35   |     | 34  |
| W                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| X                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| Y                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| Z                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| -                          |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| unknown (?)                |     |     |     |     |     |     |      |      |     |      |      |     |     |     |      |     |     |      |     |     |
| not sequenced <sup>2</sup> | 15  | 15  | 15  | 13  | 13  | 13  | 13   | 13   | 6   | 5    | 5    | 5   | 5   | 5   | 5    | 5   | 5   | 5    | 5   | 5   |
| sum of seq <sup>3</sup>    | 25  | 25  | 25  | 27  | 27  | 27  | 27   | 27   | 34  | 35   | 35   | 35  | 35  | 35  | 35   | 35  | 35  | 35   | 35  | 35  |
| oomcaa <sup>3</sup>        | 21  | 21  | 20  | 26  | 20  | 26  | 27   | 27   | 32  | 35   | 35   | 34  | 33  | 33  | 35   | 34  | 34  | 35   | 33  | 34  |
| mcaa <sup>4</sup>          | Q   | V   | Q   | L   | V   | Q   | S    | G    | A   | E    | V    | K   | K   | P   | G    | A   | S   | V    | K   | V   |
| rel. oomcaa <sup>5</sup>   | 84% | 84% | 80% | 96% | 74% | 96% | 100% | 100% | 94% | 100% | 100% | 97% | 94% | 94% | 100% | 97% | 97% | 100% | 94% | 97% |
| pos occupied <sup>6</sup>  | 3   | 3   | 4   | 2   | 4   | 2   | 1    | 1    | 3   | 1    | 1    | 2   | 2   | 3   | 1    | 2   | 2   | 1    | 2   | 2   |

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Table 6B: Analysis of V heavy chain subgroup 1B

| amino acid <sup>1</sup>   |      |      |     |     |      |      |     |     |     |     | CDRI |      |      |     |     |     |     |      |     |     |    |    |
|---------------------------|------|------|-----|-----|------|------|-----|-----|-----|-----|------|------|------|-----|-----|-----|-----|------|-----|-----|----|----|
|                           | 21   | 22   | 23  | 24  | 25   | 26   | 27  | 28  | 29  | 30  | 31   | A    | B    | 32  | 33  | 34  | 35  | 36   | 37  | 38  |    |    |
| A                         |      |      |     | 30  |      |      |     |     |     |     | 2    |      |      |     | 6   |     |     |      |     |     |    |    |
| B                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |    |    |
| C                         |      | 35   |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |    |    |
| D                         |      |      |     |     |      |      |     |     |     |     | 1    |      |      |     | 5   |     | 1   |      |     |     | 1  |    |
| E                         |      |      | 3   |     |      |      |     |     |     |     | 1    |      |      |     |     |     |     |      |     |     |    |    |
| F                         |      |      |     |     |      |      | 2   | 39  |     |     |      |      |      | 2   | 2   |     |     |      |     |     |    |    |
| G                         |      |      |     | 1   | 40   |      |     |     |     | 1   | 14   |      |      |     | 1   |     |     |      |     |     | 1  |    |
| H                         |      |      |     |     |      |      |     |     |     |     |      |      |      | 3   | 1   |     | 34  |      |     |     |    |    |
| I                         |      |      |     |     |      |      | 1   |     | 1   |     |      |      |      |     |     | 9   |     |      |     |     |    |    |
| K                         |      |      | 28  |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |    |    |
| L                         |      |      |     |     |      |      |     |     | 1   |     | 1    |      |      |     |     | 5   |     |      |     | 2   |    |    |
| M                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     | 23  |     |      |     |     |    |    |
| N                         |      |      |     |     |      |      | 1   |     |     | 1   | 3    |      |      |     |     | 1   | 3   |      |     |     |    |    |
| P                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     | 1   |     |      |     |     |    |    |
| Q                         |      |      | 2   |     |      |      |     |     |     |     | 1    |      |      |     | 1   |     | 1   |      |     |     | 1  |    |
| R                         |      |      | 2   |     |      |      |     | 2   |     |     |      |      |      |     | 1   |     |     |      |     |     | 37 |    |
| S                         | 35   |      |     | 40  |      |      | 5   | 2   | 15  |     |      |      |      | 2   | 1   |     |     |      |     |     |    |    |
| T                         |      |      | 3   |     |      |      | 32  | 34  |     |     |      |      |      |     | 1   |     |     |      |     |     |    |    |
| V                         |      |      | 1   |     |      |      | 1   |     |     | 1   | 1    |      |      |     | 2   | 2   |     |      |     | 38  |    |    |
| W                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     | 40   |     |     |    |    |
| X                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |    |    |
| Y                         |      |      |     |     |      |      | 36  |     |     |     | 1    |      |      | 32  | 19  |     | 1   |      |     |     |    |    |
| Z                         |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |    |    |
| -                         |      |      |     |     |      |      |     |     |     |     | 40   | 40   |      |     |     |     |     |      |     |     |    |    |
| unknown (?)               |      |      |     |     |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |    |    |
| not sequenced             | 5    | 5    | 5   | 5   |      |      |     |     |     |     |      |      |      |     |     |     |     |      |     |     |    |    |
| sum of seq <sup>2</sup>   | 35   | 35   | 35  | 35  | 40   | 40   | 40  | 40  | 40  | 40  | 40   | 40   | 40   | 40  | 40  | 40  | 40  | 40   | 40  | 40  | 40 | 40 |
| oomcaa <sup>3</sup>       | 35   | 35   | 28  | 30  | 40   | 40   | 36  | 32  | 39  | 34  | 15   | 40   | 40   | 32  | 19  | 23  | 34  | 40   | 38  | 37  |    |    |
| mcaa <sup>4</sup>         | S    | C    | K   | A   | S    | G    | Y   | T   | F   | T   | S    | -    | -    | Y   | Y   | M   | H   | W    | V   | R   |    |    |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 80% | 86% | 100% | 100% | 90% | 80% | 98% | 85% | 38%  | 100% | 100% | 80% | 48% | 58% | 85% | 100% | 95% | 93% |    |    |
| pos occupied <sup>6</sup> | 1    | 1    | 4   | 4   | 1    | 1    | 4   | 4   | 2   | 6   | 10   | 1    | 1    | 5   | 11  | 5   | 5   | 1    | 2   | 4   |    |    |

Table 6B: Analysis of V heavy chain subgroup 1B

|                           | Framework II |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|--|--|--|--|
| amino acid <sup>1</sup>   | 39           | 40  | 41  | 42  | 43  | 44  | 45  | 46  | 47   | 48  | 49  | 50  | 51  | 52  | A   | B    | C    | 53  | 54  | 55  |  |  |  |  |
| A                         |              | 39  |     |     |     | 1   |     |     |      |     | 1   |     |     |     | 7   |      |      | 1   |     |     |  |  |  |  |
| B                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| C                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| D                         |              |     |     |     |     |     |     |     |      |     |     |     |     | 1   |     |      |      |     | 1   |     |  |  |  |  |
| E                         |              |     |     | 1   |     |     |     | 39  |      |     |     |     |     |     |     |      |      | 1   | 1   |     |  |  |  |  |
| F                         |              |     |     |     |     |     | 2   |     |      |     |     |     | 1   |     |     |      |      | 1   |     |     |  |  |  |  |
| G                         |              |     |     | 39  |     | 28  |     |     |      |     | 39  | 1   |     |     | 1   |      |      | 9   | 1   | 39  |  |  |  |  |
| H                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      | 2   |     |     |  |  |  |  |
| I                         |              |     |     |     |     |     |     |     |      | 3   |     |     | 34  |     |     |      |      |     |     |     |  |  |  |  |
| K                         |              |     |     |     | 1   |     |     |     |      |     |     |     |     |     |     |      |      |     | 1   |     |  |  |  |  |
| L                         |              |     | 1   |     |     |     | 37  |     |      |     |     |     | 1   |     |     |      |      |     |     |     |  |  |  |  |
| M                         |              |     |     |     |     |     |     |     |      | 37  |     | 2   | 4   |     |     |      |      |     |     |     |  |  |  |  |
| N                         |              |     |     |     |     |     |     |     |      |     |     |     |     | 35  |     |      |      | 20  | 12  | 1   |  |  |  |  |
| P                         |              | 1   | 34  |     |     |     | 1   |     |      |     |     |     |     |     | 31  |      |      |     |     |     |  |  |  |  |
| Q                         | 39           |     |     |     | 39  |     |     | 1   |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| R                         | 1            |     |     |     |     | 10  |     |     |      |     |     | 4   |     |     |     |      |      | 3   | 1   |     |  |  |  |  |
| S                         |              |     | 1   |     |     | 1   |     |     |      |     |     |     |     | 2   |     |      |      | 1   | 20  |     |  |  |  |  |
| T                         |              |     | 4   |     |     |     |     |     |      |     |     |     |     | 1   |     |      |      |     | 3   |     |  |  |  |  |
| V                         |              |     |     |     |     |     |     |     |      |     |     |     |     | 1   | 1   |      |      |     |     |     |  |  |  |  |
| W                         |              |     |     |     |     |     |     |     | 40   |     |     | 33  |     |     |     |      |      |     |     |     |  |  |  |  |
| X                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| Y                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     | 2   |     |  |  |  |  |
| Z                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| -                         |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      | 40   | 40  |     |     |  |  |  |  |
| unknown (?)               |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| not sequenced             |              |     |     |     |     |     |     |     |      |     |     |     |     |     |     |      |      |     |     |     |  |  |  |  |
| sum of seq <sup>2</sup>   | 40           | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40   | 40  | 40  | 40  |  |  |  |  |
| oomcaa <sup>3</sup>       | 39           | 39  | 34  | 39  | 39  | 28  | 37  | 39  | 40   | 37  | 39  | 33  | 34  | 35  | 31  | 40   | 40   | 20  | 20  | 39  |  |  |  |  |
| mcaa <sup>4</sup>         | Q            | A   | P   | G   | Q   | G   | L   | E   | W    | M   | G   | W   | I   | N   | P   | -    | -    | N   | S   | G   |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 98%          | 98% | 85% | 98% | 98% | 70% | 93% | 98% | 100% | 93% | 98% | 83% | 85% | 88% | 78% | 100% | 100% | 50% | 50% | 98% |  |  |  |  |
| pos occupied <sup>6</sup> | 2            | 2   | 4   | 2   | 2   | 4   | 3   | 2   | 1    | 2   | 2   | 4   | 4   | 5   | 4   | 1    | 1    | 9   | 8   | 2   |  |  |  |  |

Table 68: Analysis of V heavy chain subgroup 1B

| CDR II                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 56  | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70   | 71  | 72  | 73  | 74  | 75  |
| A                         | 1   | 2   |     |     | 27  | 2   |     |     |     | 1   |     | 1   |     |     |      | 2   |     |     |     | 12  |
| B                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| C                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| D                         | 1   |     |     |     |     |     |     |     |     | 4   |     |     |     |     |      |     | 35  |     |     |     |
| E                         | 2   |     | 2   |     |     | 1   |     |     |     | 1   |     |     |     |     |      | 1   |     |     |     |     |
| F                         |     |     |     | 4   |     |     |     | 39  |     |     |     |     |     | 3   |      |     |     |     |     |     |
| G                         | 15  |     | 6   |     | 1   |     |     |     |     | 34  |     |     |     |     |      |     |     |     |     |     |
| H                         |     |     | 1   | 1   |     |     |     |     |     |     |     |     |     |     |      |     | 1   |     |     |     |
| I                         |     | 1   | 1   |     |     |     |     |     |     |     |     | 1   | 1   | 13  |      |     |     |     |     | 22  |
| K                         | 2   | 2   | 8   |     |     |     | 36  |     | 1   |     |     |     |     |     |      | 1   |     |     |     |     |
| L                         |     |     |     |     |     | 1   |     | 1   |     |     |     |     |     | 1   |      |     |     |     |     |     |
| M                         |     |     |     |     |     |     |     |     |     |     |     |     |     | 23  |      |     |     | 1   |     | 1   |
| N                         | 17  |     | 18  |     |     |     | 1   |     |     |     |     |     |     |     |      |     | 4   |     |     |     |
| P                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     | 3   |     |
| Q                         |     |     |     |     |     | 36  |     |     | 37  |     |     |     |     |     |      |     |     |     |     |     |
| R                         |     |     | 2   |     |     |     | 1   |     | 2   | 37  |     |     |     |     |      | 34  |     | 1   |     |     |
| S                         | 1   |     |     | 2   | 11  |     | 1   |     |     |     |     |     |     |     |      | 1   |     |     | 37  |     |
| T                         |     | 35  | 2   |     | 1   |     | 1   |     |     |     |     |     | 39  |     | 40   | 1   |     | 38  |     | 5   |
| V                         | 1   |     |     |     |     |     |     |     |     |     |     | 38  |     |     |      |     |     |     |     |     |
| W                         |     |     |     |     |     |     |     |     |     | 3   |     |     |     |     |      |     |     |     |     |     |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| Y                         |     |     |     | 33  |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| Z                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| -                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| not sequenced             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40  | 40  | 40  | 40  | 40  |
| oomcaa <sup>3</sup>       | 17  | 35  | 18  | 33  | 27  | 36  | 36  | 39  | 37  | 34  | 37  | 38  | 39  | 23  | 40   | 34  | 35  | 38  | 37  | 22  |
| mcaa <sup>4</sup>         | N   | T   | N   | Y   | A   | Q   | K   | F   | Q   | G   | R   | V   | T   | M   | T    | R   | D   | T   | S   | I   |
| rel. oomcaa <sup>5</sup>  | 43% | 88% | 45% | 83% | 68% | 90% | 90% | 98% | 93% | 85% | 93% | 95% | 98% | 58% | 100% | 85% | 88% | 95% | 93% | 55% |
| pos occupied <sup>6</sup> | 8   | 4   | 8   | 4   | 4   | 4   | 5   | 2   | 3   | 4   | 2   | 3   | 2   | 4   | 1    | 6   | 3   | 3   | 2   | 4   |

Table 6B: Analysis of V heavy chain subgroup 1B

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|-----|-----|-----|
|                           | 76            | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C   | 83  | 84  | 85  | 86   | 87   | 88   | 89  | 90  | 91  | 92  |
| A                         |               |     | 35  |     |     |     |     |     |     |     |     | 1   | 2   |      |      | 40   |     |     |     |     |
| B                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| C                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     | 37  |
| D                         | 1             |     |     |     |     | 4   |     |     |     |     |     |     | 19  | 40   |      |      | 1   |     |     |     |
| E                         |               |     |     |     |     | 35  |     |     |     |     |     |     | 19  |      |      |      |     |     |     |     |
| F                         |               |     | 1   |     |     |     |     |     |     |     |     | 2   |     |      |      |      |     |     | 2   | 1   |
| G                         |               |     |     |     |     | 1   |     | 1   | 2   |     |     |     |     |      |      |      |     |     |     |     |
| H                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| I                         |               | 1   |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 1   |     |     |     |
| K                         |               |     |     |     |     |     |     |     |     |     | 1   |     |     |      |      |      |     |     |     |     |
| L                         |               |     |     |     | 2   | 39  |     |     |     | 39  |     |     |     |      |      |      | 2   |     |     | 1   |
| M                         |               |     |     |     | 37  |     | 1   |     |     |     |     |     |     |      |      |      | 2   |     |     |     |
| N                         | 7             |     |     |     |     |     |     | 1   | 2   |     |     |     |     |      |      |      |     |     |     |     |
| P                         |               |     |     |     |     |     |     |     |     |     |     | 1   |     |      |      |      |     |     | 1   |     |
| Q                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| R                         | 4             |     |     |     |     |     |     | 2   | 16  |     | 37  |     |     |      |      |      |     |     |     |     |
| S                         | 27            |     |     | 1   |     |     |     | 35  | 20  |     | 1   | 36  |     |      |      |      |     | 1   | 1   |     |
| T                         | 1             | 39  |     |     |     |     |     | 1   |     |     | 1   |     |     |      | 40   |      |     |     |     |     |
| V                         |               |     | 4   |     | 1   |     |     |     |     | 1   |     |     |     |      |      |      | 33  |     |     |     |
| W                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| X                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| Y                         |               |     |     | 39  |     |     |     |     |     |     |     |     |     |      |      |      |     | 38  | 35  |     |
| Z                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| -                         |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| unknown (?)               |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |
| not sequenced             |               |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     | 1   | 1   | 1   |
| sum of seq <sup>2</sup>   | 40            | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40   | 40   | 40   | 39  | 39  | 39  | 39  |
| oomcaa <sup>3</sup>       | 27            | 39  | 35  | 39  | 37  | 35  | 39  | 35  | 20  | 39  | 37  | 36  | 19  | 40   | 40   | 40   | 33  | 38  | 35  | 37  |
| mcaa <sup>4</sup>         | S             | T   | A   | Y   | M   | E   | L   | S   | S   | L   | R   | S   | D   | D    | T    | A    | V   | Y   | Y   | C   |
| rel. oomcaa <sup>5</sup>  | 68%           | 98% | 88% | 98% | 93% | 88% | 98% | 88% | 50% | 98% | 93% | 90% | 48% | 100% | 100% | 100% | 85% | 97% | 90% | 95% |
| pos occupied <sup>6</sup> | 5             | 2   | 3   | 2   | 3   | 3   | 2   | 5   | 4   | 2   | 4   | 4   | 3   | 1    | 1    | 1    | 5   | 2   | 4   | 3   |

Table 6B: Analysis of V heavy chain subgroup 1B

| CDR III                   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 93  | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   |
| A                         | 37  | 1   | 6   |     | 1   | 1   |     | 2   | 3   | 1   | 3   |     | 1   |     |     |     |     | 5   |     |
| B                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |     | 1   |     |     |     | 3   |     |     |     | 2   | 1   |     |     |     |     |     |     |     |     |
| D                         |     |     | 7   |     | 5   | 2   | 3   | 1   | 5   | 4   |     | 1   |     | 2   | 2   | 1   | 2   |     | 27  |
| E                         |     |     | 2   |     | 1   |     |     | 1   | 1   |     | 2   |     | 1   |     | 1   |     |     |     |     |
| F                         |     |     |     | 1   | 1   | 3   |     |     | 2   | 1   | 1   | 1   | 1   |     |     |     |     | 2   | 15  |
| G                         |     | 1   | 7   | 7   | 5   | 5   | 9   | 4   | 7   | 1   | 3   |     | 2   | 2   | 1   |     | 1   | 3   | 1   |
| H                         |     |     | 1   |     |     |     | 2   |     |     | 1   | 1   |     |     |     |     |     |     |     |     |
| I                         |     | 1   |     | 1   | 1   | 3   | 1   | 1   | 1   | 1   | 1   | 1   |     |     |     |     |     |     | 1   |
| K                         |     | 1   |     |     | 1   |     |     |     | 1   | 1   |     | 1   |     | 1   |     |     | 1   |     |     |
| L                         |     |     | 2   | 4   | 4   | 4   | 3   |     |     | 1   | 2   | 1   | 1   | 2   |     | 1   |     |     | 2   |
| M                         |     |     |     | 2   |     | 1   | 1   |     |     |     |     |     |     |     | 1   |     |     |     | 4   |
| N                         |     |     |     |     | 1   |     |     | 1   |     | 1   | 1   | 1   |     |     | 3   |     | 1   |     | 1   |
| P                         |     |     |     | 6   | 4   |     |     |     | 1   | 1   |     | 3   | 2   |     |     |     | 1   |     |     |
| Q                         |     |     |     |     | 1   |     |     |     |     |     |     | 1   | 2   | 1   |     |     |     |     |     |
| R                         | 1   | 31  |     | 5   | 1   | 1   | 3   |     |     |     |     | 1   |     | 1   |     |     |     | 1   |     |
| S                         |     | 1   | 3   | 3   | 1   | 4   | 3   | 6   | 3   | 2   | 2   | 1   |     | 1   |     |     |     |     |     |
| T                         |     | 2   | 1   | 1   | 2   | 2   | 1   | 5   | 1   | 1   | 1   |     | 1   |     |     | 1   |     | 1   |     |
| V                         | 1   |     | 7   | 1   | 1   |     | 1   | 3   | 1   | 2   |     | 1   |     |     | 1   | 2   | 1   |     | 1   |
| W                         |     |     | 1   |     | 1   |     | 2   | 2   |     | 1   | 1   |     |     |     |     | 1   |     | 4   |     |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |     |     |     | 5   | 5   | 4   | 2   | 3   |     | 4   | 3   | 3   | 2   | 1   | 2   | 5   | 6   | 2   |     |
| Z                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |     |     |     | 1   | 1   | 4   | 6   | 8   | 10  | 11  | 14  | 20  | 23  | 25  | 25  | 25  | 23  | 18  | 11  |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 6   |
| not sequenced             | 1   | 1   | 3   | 3   | 3   | 3   | 3   | 3   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   |
| sum of seq <sup>2</sup>   | 39  | 39  | 37  | 37  | 37  | 37  | 37  | 37  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  | 36  |
| oomcaa <sup>3</sup>       | 37  | 31  | 7   | 7   | 5   | 5   | 9   | 8   | 10  | 11  | 14  | 20  | 23  | 25  | 25  | 25  | 23  | 18  | 15  |
| mcaa <sup>4</sup>         | A   | R   | D   | G   | D   | G   | G   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | F   |
| rel. oomcaa <sup>5</sup>  | 95% | 79% | 19% | 19% | 14% | 14% | 24% | 22% | 28% | 31% | 39% | 56% | 64% | 69% | 69% | 69% | 64% | 50% | 42% |
| pos occupied <sup>6</sup> | 3   | 8   | 10  | 12  | 18  | 13  | 13  | 12  | 12  | 17  | 14  | 13  | 10  | 9   | 8   | 7   | 8   | 8   | 5   |



Table 6B: Analysis of V heavy chain subgroup 1B

| Framework IV              |     |      |      |     |      |      |     |      |     |     |     |      |     | sum |
|---------------------------|-----|------|------|-----|------|------|-----|------|-----|-----|-----|------|-----|-----|
| amino acid <sup>1</sup>   | 102 | 103  | 104  | 105 | 106  | 107  | 108 | 109  | 110 | 111 | 112 | 113  |     |     |
| A                         |     |      |      |     |      |      |     |      |     |     |     |      | 340 |     |
| B                         |     |      |      |     |      |      |     |      |     |     |     |      |     |     |
| C                         |     |      |      |     |      |      |     |      |     |     |     |      | 79  |     |
| D                         | 2   |      |      |     |      |      |     |      |     |     |     |      | 179 |     |
| E                         |     |      |      | 1   |      |      |     |      |     |     |     |      | 159 |     |
| F                         | 1   |      |      |     |      |      |     |      |     |     |     |      | 130 |     |
| G                         |     |      | 27   |     | 26   |      |     |      |     | 1   |     |      | 450 |     |
| H                         | 1   |      |      |     |      |      |     |      |     |     |     |      | 51  |     |
| I                         | 7   |      |      |     |      |      |     |      | 3   |     |     |      | 113 |     |
| K                         |     |      |      | 2   |      |      |     |      |     |     |     |      | 194 |     |
| L                         |     |      |      |     |      |      | 12  |      |     | 1   |     |      | 204 |     |
| M                         |     |      |      |     |      |      | 2   |      |     |     |     |      | 144 |     |
| N                         | 1   |      |      |     |      |      |     |      |     |     |     |      | 138 |     |
| P                         | 1   |      |      | 1   |      |      |     |      |     |     |     |      | 128 |     |
| Q                         |     |      |      | 23  |      |      |     |      |     |     |     |      | 253 |     |
| R                         |     |      |      |     |      |      | 1   |      |     |     |     |      | 247 |     |
| S                         | 3   |      |      |     |      |      |     |      | 1   |     | 18  | 18   | 432 |     |
| T                         |     |      |      |     |      | 21   | 6   |      | 16  |     | 1   |      | 390 |     |
| V                         | 6   |      |      |     |      |      |     | 21   |     | 18  |     |      | 342 |     |
| W                         |     | 29   |      |     |      |      |     |      |     |     |     |      | 158 |     |
| X                         |     |      |      |     |      |      |     |      |     |     |     |      |     |     |
| Y                         | 11  |      |      |     |      |      |     |      |     |     |     |      | 294 |     |
| Z                         |     |      |      |     |      |      |     |      |     |     |     |      |     |     |
| -                         | 3   |      |      |     |      |      |     |      |     |     |     |      | 394 |     |
| unknown (?)               |     |      |      |     |      |      |     |      |     |     |     |      | 3   |     |
| not sequenced             | 4   | 11   | 13   | 13  | 14   | 19   | 19  | 19   | 20  | 20  | 21  | 22   | 458 |     |
| sum of seq <sup>2</sup>   | 36  | 29   | 27   | 27  | 26   | 21   | 21  | 21   | 20  | 20  | 19  | 18   |     |     |
| oomcaa <sup>3</sup>       | 11  | 29   | 27   | 23  | 26   | 21   | 12  | 21   | 16  | 18  | 18  | 18   |     |     |
| mcaa <sup>4</sup>         | Y   | W    | G    | Q   | G    | T    | L   | V    | T   | V   | S   | S    |     |     |
| rel. oomcaa <sup>5</sup>  | 31% | 100% | 100% | 85% | 100% | 100% | 57% | 100% | 80% | 90% | 95% | 100% |     |     |
| pos occupied <sup>6</sup> | 10  | 1    | 1    | 4   | 1    | 1    | 4   | 1    | 3   | 3   | 2   | 1    |     |     |

Table 6C: Analysis of V heavy chain subgroup 2

| amino acid <sup>1</sup>   | Framework I |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
|---------------------------|-------------|-----|------|------|-----|------|-----|------|------|-----|------|------|------|------|-----|-----|-----|------|------|------|
|                           | 1           | 2   | 3    | 4    | 5   | 6    | 7   | 8    | 9    | 10  | 11   | 12   | 13   | 14   | 15  | 16  | 17  | 18   | 19   | 20   |
| A                         |             |     |      |      |     |      |     |      |      | 3   |      |      |      |      |     |     |     |      |      |      |
| B                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| C                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| D                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| E                         | 1           |     |      |      |     | 6    |     |      |      |     |      |      |      |      |     | 2   |     |      |      |      |
| F                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| G                         |             |     |      |      |     |      |     | 6    |      |     |      |      |      |      |     |     |     |      |      |      |
| H                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| I                         |             | 1   |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| K                         |             |     |      |      | 3   |      |     |      |      |     |      |      | 6    |      | 1   |     |     |      |      |      |
| L                         |             |     |      | 6    |     |      |     |      |      | 6   |      |      |      |      |     |     |     | 6    |      | 6    |
| M                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| N                         |             |     |      |      |     |      | 1   |      |      |     |      |      |      |      |     |     |     |      |      |      |
| P                         |             |     |      |      |     |      | 1   |      | 6    |     |      |      | 6    |      |     |     | 1   |      |      |      |
| Q                         | 2           |     |      |      |     |      |     |      |      |     |      |      |      | 6    |     |     |     |      |      |      |
| R                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     | 4   |     |      |      |      |
| S                         |             |     |      |      |     | 2    |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| T                         |             |     |      |      |     |      | 4   |      |      |     |      |      |      |      |     |     |     |      |      |      |
| V                         |             | 5   |      |      | 1   |      |     |      |      | 2   |      |      |      |      | 5   |     | 5   |      | 6    |      |
| W                         |             |     |      |      |     |      |     |      |      | 1   |      | 6    |      |      |     |     |     |      |      |      |
| X                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| Y                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| Z                         | 3           |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| -                         |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| unknown (?)               |             |     |      |      |     |      |     |      |      |     |      |      |      |      |     |     |     |      |      |      |
| not sequenced             | 1           | 1   | 1    | 1    | 1   | 1    | 1   | 1    | 1    | 1   | 1    | 1    | 1    | 1    | 1   | 1   | 1   | 1    | 1    | 1    |
| sum of seq <sup>2</sup>   | 6           | 6   | 6    | 6    | 6   | 6    | 6   | 6    | 6    | 6   | 6    | 6    | 6    | 6    | 6   | 6   | 6   | 6    | 6    | 6    |
| oomcaa <sup>3</sup>       | 3           | 5   | 6    | 6    | 3   | 6    | 4   | 6    | 6    | 3   | 6    | 6    | 6    | 6    | 5   | 4   | 5   | 6    | 6    | 6    |
| mcaa <sup>4</sup>         | Z           | V   | T    | L    | K   | E    | S   | G    | P    | A   | L    | V    | K    | P    | T   | Q   | T   | L    | T    | L    |
| rel. oomcaa <sup>5</sup>  | 50%         | 83% | 100% | 100% | 50% | 100% | 67% | 100% | 100% | 50% | 100% | 100% | 100% | 100% | 83% | 67% | 83% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 3           | 2   | 1    | 1    | 3   | 1    | 3   | 1    | 1    | 3   | 1    | 1    | 1    | 1    | 2   | 2   | 2   | 1    | 1    | 1    |

Table 6C: Analysis of V heavy chain subgroup 2

| amino acid <sup>1</sup>   |      |      |     |     |     |      |     |     |     |     | CDRI |     |     |     |     |      |     |      |      |      |
|---------------------------|------|------|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|------|------|------|
|                           | 21   | 22   | 23  | 24  | 25  | 26   | 27  | 28  | 29  | 30  | 31   | A   | B   | 32  | 33  | 34   | 35  | 36   | 37   | 38   |
| A                         |      |      |     |     |     |      |     | 1   |     |     |      | 1   |     |     | 1   |      |     |      |      |      |
| B                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| C                         |      | 7    |     |     |     |      |     |     |     |     |      |     |     |     | 2   |      |     |      |      |      |
| D                         |      |      |     |     |     |      |     |     |     |     |      | 1   |     |     |     |      |     |      |      |      |
| E                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| F                         |      |      |     | 3   |     |      | 6   |     | 1   |     |      |     |     |     |     |      |     |      |      |      |
| G                         |      |      |     |     |     | 7    |     |     |     |     |      | 4   |     | 3   |     | 3    |     |      |      |      |
| H                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| I                         |      |      |     |     |     |      |     |     |     |     |      |     | 1   |     |     |      |     |      | 7    |      |
| K                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| L                         |      |      |     | 2   |     |      | 1   |     | 6   |     |      |     |     |     |     |      |     |      |      |      |
| M                         |      |      |     |     |     |      |     |     |     |     |      |     |     | 5   |     |      |     |      |      |      |
| N                         |      |      |     |     |     |      |     |     |     |     | 2    |     |     |     |     |      |     |      |      |      |
| P                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| Q                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| R                         |      |      |     |     |     |      |     |     |     |     |      |     | 2   |     | 1   |      |     |      |      | 7    |
| S                         |      |      | 1   |     | 6   |      |     | 6   |     | 6   | 2    | 4   |     |     |     |      | 4   |      |      |      |
| T                         | 6    |      | 6   |     |     |      |     |     |     | 1   | 3    | 1   |     |     |     |      |     |      |      |      |
| V                         |      |      |     | 2   |     |      |     |     |     |     |      |     |     | 2   |     | 7    |     |      |      |      |
| W                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     | 7    |      |      |
| X                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| Y                         |      |      |     |     | 1   |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| Z                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| -                         |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| unknown (?)               |      |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| not sequenced             | 1    |      |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |      |      |      |
| sum of seq <sup>2</sup>   | 6    | 7    | 7   | 7   | 7   | 7    | 7   | 7   | 7   | 7   | 7    | 7   | 7   | 7   | 7   | 7    | 7   | 7    | 7    | 7    |
| oomcaa <sup>3</sup>       | 6    | 7    | 6   | 3   | 6   | 7    | 6   | 6   | 6   | 6   | 3    | 4   | 4   | 5   | 3   | 7    | 4   | 7    | 7    | 7    |
| mcaa <sup>4</sup>         | T    | C    | T   | F   | S   | G    | F   | S   | L   | S   | T    | S   | G   | M   | G   | V    | S   | W    | I    | R    |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 86% | 43% | 86% | 100% | 86% | 86% | 86% | 86% | 43%  | 57% | 57% | 71% | 43% | 100% | 57% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 1    | 1    | 2   | 3   | 2   | 1    | 2   | 2   | 2   | 2   | 3    | 4   | 3   | 2   | 4   | 1    | 2   | 1    | 1    | 1    |

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Table 6C: Analysis of V heavy chain subgroup 2

| amino acid <sup>1</sup>   | Framework II |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      | A   | B   | C   | 53 | 54 | 55 |
|---------------------------|--------------|-----|------|------|-----|-----|------|------|------|------|------|-----|-----|-----|-----|------|------|-----|-----|-----|----|----|----|
|                           | 39           | 40  | 41   | 42   | 43  | 44  | 45   | 46   | 47   | 48   | 49   | 50  | 51  | 52  |     |      |      |     |     |     |    |    |    |
| A                         |              |     |      |      |     | 6   |      |      |      |      | 7    |     |     |     |     |      |      |     |     |     |    |    |    |
| B                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| C                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| D                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 2   |     |      |      |     |     |     |    | 3  | 6  |
| E                         |              |     |      |      |     |     |      | 7    |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| F                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 2   |     |      |      |     |     |     |    |    |    |
| G                         |              | 1   |      | 7    |     | 1   |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| H                         |              |     |      |      |     |     |      |      |      |      |      | 2   |     |     |     |      |      |     |     |     |    |    | 1  |
| I                         |              |     |      |      |     |     |      |      |      |      |      |     | 6   |     |     |      |      |     |     |     |    |    |    |
| K                         |              |     |      |      | 6   |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| L                         |              |     |      |      |     |     | 7    |      |      | 7    |      | 2   | 1   | 1   |     |      |      |     |     |     |    |    |    |
| M                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| N                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    | 3  |    |
| P                         |              | 5   | 7    |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| Q                         | 6            |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| R                         | 1            |     |      |      | 1   |     |      |      |      |      |      | 2   |     |     |     |      |      |     |     |     |    |    |    |
| S                         |              | 1   |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     | 2  |    |    |
| T                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| V                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| W                         |              |     |      |      |     |     |      |      | 7    |      |      | 1   |     |     |     |      |      |     |     |     | 4  |    |    |
| X                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 1   |     |      |      |     |     |     | 1  | 1  |    |
| Y                         |              |     |      |      |     |     |      |      |      |      |      |     |     | 1   | 1   |      |      |     |     |     |    |    |    |
| Z                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| -                         |              |     |      |      |     |     |      |      |      |      |      |     |     |     | 6   | 7    | 7    |     |     |     |    |    |    |
| unknown (?)               |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| not sequenced             |              |     |      |      |     |     |      |      |      |      |      |     |     |     |     |      |      |     |     |     |    |    |    |
| sum of seq <sup>2</sup>   | 7            | 7   | 7    | 7    | 7   | 7   | 7    | 7    | 7    | 7    | 7    | 7   | 7   | 7   | 7   | 7    | 7    | 7   | 7   | 7   | 7  | 7  | 7  |
| oomcaa <sup>3</sup>       | 6            | 5   | 7    | 7    | 6   | 6   | 7    | 7    | 7    | 7    | 7    | 2   | 6   | 2   | 6   | 7    | 7    | 4   | 3   | 6   |    |    |    |
| mcaa <sup>4</sup>         | Q            | P   | P    | G    | K   | A   | L    | E    | W    | L    | A    | H   | I   | D   | -   | -    | -    | W   | D   | D   |    |    |    |
| rel. oomcaa <sup>5</sup>  | 86%          | 71% | 100% | 100% | 86% | 86% | 100% | 100% | 100% | 100% | 100% | 29% | 86% | 29% | 86% | 100% | 100% | 57% | 43% | 86% |    |    |    |
| pos occupied <sup>6</sup> | 2            | 3   | 1    | 1    | 2   | 2   | 1    | 1    | 1    | 1    | 1    | 4   | 2   | 5   | 2   | 1    | 1    | 3   | 3   | 2   |    |    |    |

Table 6C: Analysis of V heavy chain subgroup 2

|                           | CDR II |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
|---------------------------|--------|-----|-----|-----|-----|-----|------|------|-----|-----|------|------|-----|-----|-----|-----|-----|-----|------|-----|--|--|--|--|--|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61  | 62   | 63   | 64  | 65  | 66   | 67   | 68  | 69  | 70  | 71  | 72  | 73  | 74   | 75  |  |  |  |  |  |
| A                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| B                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| C                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| D                         | 5      |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     | 6   | 1   |      |     |  |  |  |  |  |
| E                         | 1      |     |     |     |     |     |      |      | 1   |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| F                         |        | 1   |     | 1   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| G                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| H                         |        |     |     | 1   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| I                         |        |     |     |     |     |     |      |      |     |     |      |      |     | 6   |     |     |     |     |      |     |  |  |  |  |  |
| K                         | 1      | 6   |     |     |     |     |      |      | 4   |     |      |      |     |     |     |     | 6   |     |      | 6   |  |  |  |  |  |
| L                         |        |     |     |     |     |     |      | 7    |     |     |      | 7    |     |     |     |     |     |     |      |     |  |  |  |  |  |
| M                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| N                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     | 1   |     |      |     |  |  |  |  |  |
| P                         |        |     |     |     |     | 2   |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| Q                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| R                         |        |     | 2   |     |     | 1   |      |      | 2   |     | 7    |      |     |     |     |     | 1   |     |      | 1   |  |  |  |  |  |
| S                         |        |     | 2   |     | 6   |     | 7    |      |     | 4   |      |      | 1   |     | 5   |     |     |     | 7    |     |  |  |  |  |  |
| T                         |        |     |     |     |     | 4   |      |      |     | 3   |      |      | 6   |     | 2   |     |     | 6   |      |     |  |  |  |  |  |
| V                         |        |     |     |     |     |     |      |      |     |     |      |      |     | 1   |     |     |     |     |      |     |  |  |  |  |  |
| W                         |        |     |     | 1   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| X                         |        |     |     |     | 1   |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| Y                         |        |     | 3   | 4   |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| Z                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| -                         |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| unknown (?)               |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| not sequenced             |        |     |     |     |     |     |      |      |     |     |      |      |     |     |     |     |     |     |      |     |  |  |  |  |  |
| sum of seq <sup>2</sup>   | 7      | 7   | 7   | 7   | 7   | 7   | 7    | 7    | 7   | 7   | 7    | 7    | 7   | 7   | 7   | 7   | 7   | 7   | 7    | 7   |  |  |  |  |  |
| oomcaa <sup>3</sup>       | 5      | 6   | 3   | 4   | 6   | 4   | 7    | 7    | 4   | 4   | 7    | 7    | 6   | 6   | 5   | 6   | 6   | 6   | 7    | 6   |  |  |  |  |  |
| mcaa <sup>4</sup>         | D      | K   | Y   | Y   | S   | T   | S    | L    | K   | S   | R    | L    | T   | I   | S   | K   | D   | T   | S    | K   |  |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 71%    | 86% | 43% | 57% | 86% | 57% | 100% | 100% | 57% | 57% | 100% | 100% | 86% | 86% | 71% | 86% | 86% | 86% | 100% | 86% |  |  |  |  |  |
| pos occupied <sup>6</sup> | 3      | 2   | 3   | 4   | 2   | 3   | 1    | 1    | 3   | 2   | 1    | 1    | 2   | 2   | 2   | 2   | 2   | 2   | 1    | 2   |  |  |  |  |  |

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Table 6C: Analysis of V heavy chain subgroup 2

| Framework III             |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
|---------------------------|-----|------|------|------|-----|-----|------|-----|-----|-----|-----|------|-----|------|------|-----|------|------|------|------|
| amino acid <sup>1</sup>   | 76  | 77   | 78   | 79   | 80  | 81  | 82   | A   | B   | C   | 83  | 84   | 85  | 86   | 87   | 88  | 89   | 90   | 91   | 92   |
| A                         |     |      |      |      |     |     |      |     |     |     |     |      | 1   |      |      | 5   |      |      |      |      |
| B                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| C                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      | 7    |
| D                         |     |      |      |      |     |     |      |     |     |     | 6   |      |     | 7    |      |     |      |      |      |      |
| E                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| F                         |     |      |      |      | 1   |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| G                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      | 2   |      |      |      |      |
| H                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| I                         |     |      |      |      |     | 2   |      | 1   |     |     |     |      |     |      |      |     |      |      |      |      |
| K                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| L                         |     |      |      |      | 6   |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| M                         |     |      |      |      |     |     | 7    |     |     | 5   |     |      |     |      |      |     |      |      |      |      |
| N                         | 5   |      |      |      |     |     |      |     | 6   |     | 1   |      |     |      |      |     |      |      |      |      |
| P                         |     |      |      |      |     |     |      |     |     |     |     | 7    |     |      |      |     |      |      |      |      |
| Q                         |     | 7    |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| R                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| S                         | 2   |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| T                         |     |      |      |      |     | 5   |      | 5   |     |     |     |      |     |      | 7    |     | 7    |      |      |      |
| V                         |     |      | 7    | 7    |     |     |      |     |     | 1   |     |      | 6   |      |      |     |      |      |      |      |
| W                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| X                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| Y                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      | 7    | 7    |      |
| Z                         |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| -                         |     |      |      |      |     |     |      | 1   | 1   | 1   |     |      |     |      |      |     |      |      |      |      |
| unknown (?)               |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| not sequenced             |     |      |      |      |     |     |      |     |     |     |     |      |     |      |      |     |      |      |      |      |
| sum of seq <sup>2</sup>   | 7   | 7    | 7    | 7    | 7   | 7   | 7    | 7   | 7   | 7   | 7   | 7    | 7   | 7    | 7    | 7   | 7    | 7    | 7    | 7    |
| oomcaa <sup>3</sup>       | 5   | 7    | 7    | 7    | 6   | 5   | 7    | 5   | 6   | 5   | 6   | 7    | 6   | 7    | 7    | 5   | 7    | 7    | 7    | 7    |
| mcaa <sup>4</sup>         | N   | Q    | V    | V    | L   | T   | M    | T   | N   | M   | D   | P    | V   | D    | T    | A   | T    | Y    | Y    | C    |
| rel. oomcaa <sup>5</sup>  | 71% | 100% | 100% | 100% | 86% | 71% | 100% | 71% | 86% | 71% | 86% | 100% | 86% | 100% | 100% | 71% | 100% | 100% | 100% | 100% |
| pos occupied <sup>6</sup> | 2   | 1    | 1    | 1    | 2   | 2   | 1    | 3   | 2   | 3   | 2   | 1    | 2   | 1    | 1    | 2   | 1    | 1    | 1    | 1    |

Table 6C: Analysis of V heavy chain subgroup 2

|                           |     | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
|---------------------------|-----|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|------|
| amino acid <sup>1</sup>   | 93  | 94      | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H    | I   | J   | K   | 101  |
| A                         | 5   |         |     |     |     |     |     | 1   | 2   | 1   |     |     |     |     |     |      |     |     |     |      |
| B                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| C                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| D                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     | 6    |
| E                         |     |         |     |     |     |     |     | 2   |     |     | 1   |     |     |     |     |      |     |     |     |      |
| F                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     | 3   |      |
| G                         |     |         |     |     |     | 1   | 1   |     | 1   | 2   | 1   | 1   | 1   | 1   |     |      |     |     |     |      |
| H                         |     | 1       |     | 1   |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| I                         |     |         | 3   |     |     | 2   |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| K                         |     |         |     |     |     |     | 1   |     |     |     |     |     |     |     |     |      |     |     |     |      |
| L                         |     |         |     |     |     |     |     | 1   |     | 1   |     |     |     |     |     |      |     |     | 1   |      |
| M                         |     |         |     |     |     |     |     | 1   |     |     |     |     |     |     |     |      |     |     | 2   |      |
| N                         |     |         |     | 1   | 2   |     |     |     |     |     |     |     |     |     |     |      | 1   |     |     |      |
| P                         |     |         |     | 1   | 1   |     | 1   |     | 1   |     |     |     |     |     |     |      |     |     |     |      |
| Q                         |     |         | 1   |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| R                         |     | 6       | 1   |     |     | 1   |     |     | 1   |     |     |     |     |     |     |      |     |     |     |      |
| S                         |     |         |     | 1   |     | 1   | 1   |     |     |     |     |     |     |     |     |      |     |     |     |      |
| T                         |     |         |     | 1   |     |     | 1   |     | 1   |     |     |     |     |     |     |      |     |     |     |      |
| V                         | 2   |         | 1   | 1   | 1   |     | 1   | 1   |     |     | 1   |     |     |     |     |      |     |     |     |      |
| W                         |     |         |     |     |     | 1   |     |     |     |     |     |     |     |     |     | 1    |     | 1   |     |      |
| X                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| Y                         |     |         |     |     | 2   |     |     |     |     |     | 1   | 2   | 1   | 1   | 1   |      |     | 2   |     |      |
| Z                         |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| -                         |     |         |     |     |     |     |     |     |     | 2   | 2   | 3   | 4   | 4   | 4   | 6    | 5   | 3   |     |      |
| unknown (?)               |     |         |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |      |
| not sequenced             |     |         | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    | 1   | 1   | 1   | 1    |
| sum of seq <sup>2</sup>   | 7   | 7       | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6    | 6   | 6   | 6   | 6    |
| oomcaa <sup>3</sup>       | 5   | 6       | 3   | 1   | 2   | 2   | 1   | 2   | 2   | 2   | 2   | 3   | 4   | 4   | 4   | 6    | 5   | 3   | 3   | 6    |
| mcaa <sup>4</sup>         | A   | R       | I   | H   | N   | I   | G   | E   | A   | -   | -   | -   | -   | -   | -   | -    | -   | -   | F   | D    |
| rel. oomcaa <sup>5</sup>  | 71% | 86%     | 50% | 17% | 33% | 33% | 17% | 33% | 33% | 33% | 33% | 50% | 67% | 67% | 67% | 100% | 83% | 50% | 50% | 100% |
| pos occupied <sup>6</sup> | 2   | 2       | 4   | 6   | 4   | 5   | 6   | 5   | 5   | 4   | 5   | 3   | 3   | 3   | 3   | 1    | 2   | 3   | 3   | 1    |

Table 6C: Analysis of V heavy chain subgroup 2

| Framework IV              |     |      |      |     |      |      |     |      |     |      |      |      |     |
|---------------------------|-----|------|------|-----|------|------|-----|------|-----|------|------|------|-----|
| amino acid <sup>1</sup>   | 102 | 103  | 104  | 105 | 106  | 107  | 108 | 109  | 110 | 111  | 112  | 113  | sum |
| A                         |     |      |      |     |      |      |     |      | 1   |      |      |      | 35  |
| B                         |     |      |      |     |      |      |     |      |     |      |      |      |     |
| C                         |     |      |      |     |      |      |     |      |     |      |      |      | 16  |
| D                         |     |      |      |     |      |      |     |      |     |      |      |      | 43  |
| E                         |     |      |      |     |      |      |     |      |     |      |      |      | 21  |
| F                         |     |      |      |     |      |      |     |      |     |      |      |      | 18  |
| G                         |     |      | 6    |     | 6    |      |     |      |     |      |      |      | 55  |
| H                         |     |      |      |     |      |      |     |      |     |      |      |      | 6   |
| I                         |     |      |      |     |      |      |     |      |     |      |      |      | 29  |
| K                         |     |      |      | 1   |      |      | 1   |      |     |      |      |      | 42  |
| L                         | 1   |      |      |     |      |      | 3   |      |     |      |      |      | 78  |
| M                         |     |      |      |     |      |      |     |      |     |      |      |      | 20  |
| N                         |     |      |      |     |      |      |     |      |     |      |      |      | 23  |
| P                         | 1   |      |      |     |      |      | 1   |      |     |      |      |      | 41  |
| Q                         |     |      |      | 3   |      |      |     |      |     |      |      |      | 23  |
| R                         |     |      |      | 2   |      |      |     |      |     |      |      |      | 41  |
| S                         |     |      |      |     |      |      |     |      |     |      | 6    | 3    | 82  |
| T                         |     |      |      |     |      | 6    | 1   |      | 5   |      |      |      | 102 |
| V                         | 3   |      |      |     |      |      |     | 6    |     | 6    |      |      | 68  |
| W                         |     | 6    |      |     |      |      |     |      |     |      |      |      | 29  |
| X                         |     |      |      |     |      |      |     |      |     |      |      |      | 4   |
| Y                         | 1   |      |      |     |      |      |     |      |     |      |      |      | 35  |
| Z                         |     |      |      |     |      |      |     |      |     |      |      |      | 3   |
| -                         |     |      |      |     |      |      |     |      |     |      |      |      | 56  |
| unknown (?)               |     |      |      |     |      |      |     |      |     |      |      |      |     |
| not sequenced             | 1   | 1    | 1    | 1   | 1    | 1    | 1   | 1    | 1   | 1    | 1    | 4    | 54  |
| sum of seq <sup>2</sup>   | 6   | 6    | 6    | 6   | 6    | 6    | 6   | 6    | 6   | 6    | 6    | 3    |     |
| oomcaa <sup>3</sup>       | 3   | 6    | 6    | 3   | 6    | 6    | 3   | 6    | 5   | 6    | 6    | 3    |     |
| mcaa <sup>4</sup>         | V   | W    | G    | Q   | G    | T    | L   | V    | T   | V    | S    | S    |     |
| rel. oomcaa <sup>5</sup>  | 50% | 100% | 100% | 50% | 100% | 100% | 50% | 100% | 83% | 100% | 100% | 100% |     |
| pos occupied <sup>6</sup> | 4   | 1    | 1    | 3   | 1    | 1    | 4   | 1    | 2   | 1    | 1    | 1    |     |

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Table 6D: Analysis of V heavy chain subgroup 3

| Frame                     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8    | 9   | 10  | 11  | 12  | 13  | 14  | 15  |
| A                         |     |     |     |     | 1   |     | 1   |      |     | 12  |     | 1   |     | 3   | 1   |
| B                         |     |     | 1   |     |     | 1   |     |      |     |     |     |     | 1   |     |     |
| C                         |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| D                         | 1   |     |     |     |     | 1   |     |      |     | 16  |     |     |     |     |     |
| E                         | 110 |     | 9   |     | 15  | 166 |     |      | 9   |     |     |     | 8   |     | 2   |
| F                         |     |     |     |     |     |     |     |      |     |     | 4   |     |     |     |     |
| G                         |     |     |     |     |     |     | 181 | 193  | 174 |     |     | 1   |     |     | 202 |
| H                         |     |     | 5   |     |     |     |     |      |     |     |     |     | 4   |     |     |
| I                         |     |     |     |     |     |     |     |      |     |     |     | 9   |     |     |     |
| K                         |     | 5   | 3   |     |     |     |     |      |     |     |     |     | 26  |     |     |
| L                         |     | 1   | 5   | 176 | 43  |     |     |      |     | 140 |     |     |     | 1   |     |
| M                         |     | 12  |     | 1   |     |     |     |      |     |     |     |     |     |     |     |
| N                         |     |     |     |     |     |     |     |      |     | 1   |     |     |     |     |     |
| P                         |     |     |     |     |     |     |     |      |     |     |     |     | 1   | 194 |     |
| Q                         | 41  |     | 138 | 1   | 3   | 12  |     |      |     |     |     |     | 162 |     |     |
| R                         |     |     | 6   |     |     |     |     |      |     |     |     |     | 4   |     |     |
| S                         |     |     |     |     |     |     | 178 |      |     | 2   |     |     |     | 8   |     |
| T                         |     |     |     |     |     |     | 1   |      |     |     |     |     |     |     |     |
| V                         | 5   | 147 |     | 1   | 118 |     |     |      |     |     | 62  | 195 |     |     |     |
| W                         |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 1   |
| X                         |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Y                         |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| Z                         | 8   |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| -                         |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| unknown (?)               |     |     |     |     |     |     |     |      |     |     |     |     |     |     |     |
| not sequenced             | 47  | 47  | 45  | 33  | 32  | 32  | 32  | 31   | 10  | 7   | 6   | 6   | 6   | 6   | 6   |
| sum of seq <sup>2</sup>   | 165 | 165 | 167 | 179 | 180 | 180 | 180 | 181  | 202 | 205 | 206 | 206 | 206 | 206 | 206 |
| oomcaa <sup>3</sup>       | 110 | 147 | 138 | 176 | 118 | 166 | 178 | 181  | 193 | 174 | 140 | 195 | 162 | 194 | 202 |
| mcaa <sup>4</sup>         | E   | V   | Q   | L   | V   | E   | S   | G    | G   | G   | L   | V   | Q   | P   | G   |
| rel. oomcaa <sup>5</sup>  | 67% | 89% | 83% | 98% | 66% | 92% | 99% | 100% | 96% | 85% | 68% | 95% | 79% | 94% | 98% |
| pos occupied <sup>6</sup> | 5   | 4   | 7   | 4   | 5   | 4   | 3   | 1    | 2   | 5   | 3   | 4   | 7   | 4   | 4   |

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Table 6D: Analysis of V heavy chain subgroup 3

| work I                    |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
|---------------------------|-----|-----|-----|-----|-----|-----|------|-----|-----|------|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 16  | 17  | 18  | 19  | 20  | 21  | 22   | 23  | 24  | 25   | 26  | 27  | 28  | 29  | 30  |
| A                         |     |     |     |     |     |     |      | 183 | 192 |      | 1   |     |     |     |     |
| B                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
| C                         |     |     |     |     |     | 1   | 209  |     |     |      |     |     |     |     |     |
| D                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     | 7   |
| E                         | 8   |     |     |     |     |     |      | 8   |     |      | 3   |     | 1   |     |     |
| F                         |     | 1   | 1   |     |     | 1   |      |     |     |      |     | 201 |     | 201 |     |
| G                         | 134 |     |     |     |     |     |      |     | 2   |      | 207 |     |     |     | 3   |
| H                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     | 1   |
| I                         |     |     |     |     |     |     |      | 2   |     |      |     | 3   | 17  | 1   |     |
| K                         |     |     |     | 15  |     |     |      |     |     |      |     |     |     |     | 4   |
| L                         |     |     | 205 |     | 201 |     |      |     |     |      |     | 6   |     | 3   |     |
| M                         |     |     | 1   |     |     |     |      |     |     |      |     |     | 1   |     |     |
| N                         |     |     |     |     |     |     |      |     |     |      |     |     | 10  |     | 10  |
| P                         |     |     |     |     |     |     |      | 1   |     |      |     |     | 2   |     |     |
| Q                         |     |     | 1   |     |     |     |      |     |     |      |     |     |     |     |     |
| R                         | 62  |     |     | 191 |     |     |      |     |     |      |     |     |     |     | 11  |
| S                         |     | 206 |     |     |     | 207 |      | 4   | 2   | 209  |     |     | 15  |     | 174 |
| T                         | 4   | 1   |     | 2   |     |     |      | 4   | 4   |      |     | 1   | 163 |     |     |
| V                         |     |     |     |     | 8   |     |      | 7   | 9   |      |     |     | 1   | 6   |     |
| W                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
| X                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
| Y                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
| Z                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
| -                         |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
| unknown (?)               |     |     |     |     |     |     |      |     |     |      |     |     |     |     |     |
| not sequenced             | 4   | 4   | 4   | 4   | 3   | 3   | 3    | 3   | 3   | 3    | 1   | 1   | 2   | 1   | 2   |
| sum of seq <sup>2</sup>   | 208 | 208 | 208 | 208 | 209 | 209 | 209  | 209 | 209 | 209  | 211 | 211 | 210 | 211 | 210 |
| oomcaa <sup>3</sup>       | 134 | 206 | 205 | 191 | 201 | 207 | 209  | 183 | 192 | 209  | 207 | 201 | 163 | 201 | 174 |
| mcaa <sup>4</sup>         | G   | S   | L   | R   | L   | S   | C    | A   | A   | S    | G   | F   | T   | F   | S   |
| rel. oomcaa <sup>5</sup>  | 64% | 99% | 99% | 92% | 96% | 99% | 100% | 88% | 92% | 100% | 98% | 95% | 78% | 95% | 83% |
| pos occupied <sup>6</sup> | 4   | 3   | 4   | 3   | 2   | 3   | 1    | 7   | 5   | 1    | 3   | 4   | 8   | 4   | 7   |

Table 6D: Analysis of V heavy chain subgroup 3

|                            | CDRI |      |      |     |     |     |     |      |     |     | Frame |     |     |     |     |  |  |
|----------------------------|------|------|------|-----|-----|-----|-----|------|-----|-----|-------|-----|-----|-----|-----|--|--|
| amino acid <sup>a</sup>    | 31   | A    | B    | 32  | 33  | 34  | 35  | 36   | 37  | 38  | 39    | 40  | 41  | 42  | 43  |  |  |
| A                          | 1    |      |      | 17  | 80  |     | 1   |      |     | 1   |       | 187 |     | 1   |     |  |  |
| B                          |      |      |      |     |     |     |     |      |     |     |       |     |     |     |     |  |  |
| C                          |      |      |      |     |     |     |     |      |     |     |       | 1   |     | 1   |     |  |  |
| D                          | 26   |      |      | 3   | 7   |     | 2   |      |     |     |       |     |     |     |     |  |  |
| E                          | 1    |      |      |     | 10  |     |     |      |     |     |       |     |     | 1   | 1   |  |  |
| F                          |      |      |      | 5   |     |     |     |      |     |     |       |     |     |     |     |  |  |
| G                          | 13   |      |      |     | 31  |     | 1   |      |     |     |       | 2   |     | 209 |     |  |  |
| H                          |      |      |      | 4   |     |     | 88  |      |     |     |       |     |     |     |     |  |  |
| I                          | 1    |      |      | 1   |     | 15  |     |      | 12  |     |       |     |     |     |     |  |  |
| K                          | 7    |      |      |     |     |     |     |      |     |     | 1     |     |     |     | 202 |  |  |
| L                          | 3    |      |      |     |     | 3   |     |      | 2   | 3   | 1     | 2   | 1   |     |     |  |  |
| M                          |      |      |      |     |     | 193 |     |      |     |     |       |     |     |     |     |  |  |
| N                          | 35   |      |      | 8   | 3   |     | 34  |      |     |     |       |     |     |     |     |  |  |
| P                          |      |      |      | 1   |     |     | 1   |      |     |     |       | 4   | 191 |     |     |  |  |
| Q                          |      |      |      |     |     |     |     |      |     |     | 209   |     | 1   |     | 1   |  |  |
| R                          | 7    |      |      |     |     |     |     |      |     | 207 |       | 7   |     |     | 8   |  |  |
| S                          | 103  |      |      | 17  | 8   |     | 72  |      |     |     |       | 3   | 14  |     |     |  |  |
| T                          | 9    |      |      |     | 15  |     | 10  |      |     |     |       | 4   | 5   |     |     |  |  |
| V                          | 2    |      |      |     | 7   | 1   |     |      | 197 |     |       | 2   |     |     |     |  |  |
| W                          |      |      |      |     | 30  |     |     | 212  |     |     |       |     |     |     |     |  |  |
| X                          | 1    |      |      |     |     |     |     |      |     |     |       |     |     |     |     |  |  |
| Y                          | 1    |      |      | 154 | 19  |     | 3   |      |     |     |       |     |     |     |     |  |  |
| Z                          |      |      |      |     |     |     |     |      |     |     |       |     |     |     |     |  |  |
| -                          |      | 210  | 210  |     |     |     |     |      |     |     |       |     |     |     |     |  |  |
| unknown (?)                |      |      |      |     |     |     |     |      |     |     |       |     |     |     |     |  |  |
| not sequenced <sup>b</sup> | 2    |      |      | 2   | 2   |     |     |      | 1   | 1   | 1     |     |     |     |     |  |  |
| sum of seq <sup>c</sup>    | 210  | 210  | 210  | 210 | 210 | 212 | 212 | 212  | 211 | 211 | 211   | 212 | 212 | 212 | 212 |  |  |
| oomcaa <sup>d</sup>        | 103  | 210  | 210  | 154 | 80  | 193 | 88  | 212  | 197 | 207 | 209   | 187 | 191 | 209 | 202 |  |  |
| mcaa <sup>e</sup>          | S    | -    | -    | Y   | A   | M   | H   | W    | V   | R   | Q     | A   | P   | G   | K   |  |  |
| rel. oomcaa <sup>s</sup>   | 49%  | 100% | 100% | 73% | 38% | 91% | 42% | 100% | 93% | 98% | 99%   | 88% | 90% | 99% | 95% |  |  |
| pos occupied <sup>f</sup>  | 14   | 1    | 1    | 9   | 10  | 4   | 9   | 1    | 3   | 3   | 3     | 9   | 5   | 4   | 4   |  |  |

Table 6D: Analysis of V heavy chain subgroup 3

| work II                   |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 44  | 45   | 46  | 47  | 48  | 49  | 50  | 51  | 52  | A   | B   | C   | 53  | 54  | 55  |
| A                         | 1   |      |     |     |     | 77  | 42  |     | 1   | 2   |     | 14  |     | 7   |     |
| B                         |     |      | 3   |     |     |     |     |     |     | 1   |     |     |     |     |     |
| C                         |     |      |     |     |     |     |     |     |     |     |     |     | 1   |     |     |
| D                         |     |      | 1   |     |     |     |     |     |     | 7   |     |     | 94  | 8   | 3   |
| E                         |     |      | 198 |     |     |     |     |     | 3   | 2   | 1   |     | 2   |     | 1   |
| F                         |     |      |     |     |     |     | 7   | 1   | 2   | 1   |     |     |     | 1   | 8   |
| G                         | 207 |      |     |     |     | 33  | 11  |     | 10  | 46  |     |     | 4   | 163 | 85  |
| H                         |     |      |     |     |     |     | 6   |     |     | 1   |     |     |     |     |     |
| I                         |     |      |     |     | 3   |     | 3   | 191 |     | 1   |     |     |     |     | 1   |
| K                         |     |      |     |     |     |     |     | 1   | 37  | 2   | 30  |     | 3   | 1   |     |
| L                         |     | 211  |     |     | 5   |     | 12  | 1   |     |     |     |     |     |     |     |
| M                         |     |      |     |     |     |     | 1   | 1   |     |     |     |     |     |     |     |
| N                         |     |      |     |     |     |     | 13  |     | 7   | 9   | 2   |     | 13  | 11  | 1   |
| P                         |     | 1    |     |     |     |     |     |     |     | 1   |     |     | 1   |     |     |
| Q                         |     |      | 7   |     |     |     | 7   |     |     | 10  |     |     |     |     |     |
| R                         | 1   |      |     |     |     |     | 24  | 1   | 17  | 5   | 1   |     | 2   |     | 16  |
| S                         | 3   |      |     | 1   |     | 102 | 11  | 9   | 118 | 43  |     | 1   | 74  | 17  | 82  |
| T                         |     |      |     |     |     |     | 3   | 5   | 4   | 2   |     | 13  | 12  | 3   | 3   |
| V                         |     |      | 3   |     | 204 |     | 49  | 2   |     | 1   |     | 6   |     |     |     |
| W                         |     |      |     | 210 |     |     | 1   |     | 8   | 6   |     |     |     |     |     |
| X                         |     |      |     |     |     |     |     |     |     |     |     |     | 4   |     | 3   |
| Y                         |     |      |     | 1   |     |     | 22  |     | 5   | 58  |     |     |     |     | 8   |
| Z                         |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |     |      |     |     |     |     |     |     |     | 14  | 178 | 178 | 2   | 1   | 1   |
| unknown (?)               |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
| not sequenced             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |
| sum of seq <sup>2</sup>   | 212 | 212  | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 |
| oomcaa <sup>3</sup>       | 207 | 211  | 198 | 210 | 204 | 102 | 49  | 191 | 118 | 58  | 178 | 178 | 94  | 163 | 85  |
| mcaa <sup>4</sup>         | G   | L    | E   | W   | V   | S   | V   | I   | S   | Y   | -   | -   | D   | G   | G   |
| rel. oomcaa <sup>5</sup>  | 98% | 100% | 93% | 99% | 96% | 48% | 23% | 90% | 56% | 27% | 84% | 84% | 44% | 77% | 40% |
| pos occupied <sup>6</sup> | 4   | 2    | 5   | 3   | 3   | 3   | 15  | 9   | 11  | 19  | 5   | 5   | 12  | 9   | 12  |

Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | CDR II |     |     |     |     |     |     |     |     |      |     |     |     |     |      |     |
|---------------------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|
|                           | 56     | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65   | 66  | 67  | 68  | 69  | 70   |     |
| A                         | 9      | 1   | 2   |     | 174 | 33  |     |     |     |      |     |     |     | 1   |      |     |
| B                         | 1      | 2   |     |     |     |     |     |     |     |      |     |     |     |     |      |     |
| C                         |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |     |
| D                         | 11     |     | 17  |     |     | 160 |     |     |     |      |     |     |     |     |      |     |
| E                         | 8      | 3   | 2   |     |     | 1   |     |     | 2   |      |     |     |     |     |      |     |
| F                         | 1      |     | 3   | 2   |     |     |     |     |     |      |     | 207 |     |     |      |     |
| G                         | 5      | 1   | 5   |     | 4   | 5   |     |     |     | 212  | 1   |     |     |     |      |     |
| H                         | 1      |     | 4   |     |     |     |     |     |     |      |     |     |     |     |      |     |
| I                         | 3      | 37  | 2   |     |     |     |     | 8   |     |      |     |     | 14  | 208 |      |     |
| K                         | 1      | 61  |     |     |     |     |     |     | 199 |      | 8   |     |     |     |      |     |
| L                         | 1      | 1   | 1   |     | 1   |     |     |     |     |      |     | 1   |     | 1   |      |     |
| M                         | 8      |     | 2   |     | 1   |     |     |     |     |      |     |     |     |     |      |     |
| N                         | 51     |     | 4   |     |     | 2   |     |     | 2   |      |     |     |     |     |      |     |
| P                         | 1      | 1   |     |     | 6   | 8   | 18  |     | 1   |      |     |     |     |     |      |     |
| Q                         | 3      | 2   |     |     |     |     |     |     | 2   |      | 2   |     |     |     |      |     |
| R                         | 5      | 4   |     |     | 5   |     |     |     | 6   |      | 201 |     |     |     |      |     |
| S                         | 48     |     | 11  |     | 4   |     | 193 |     |     |      |     | 2   | 7   |     | 211  |     |
| T                         | 42     | 97  | 5   |     | 7   |     |     |     |     |      |     |     | 189 |     | 1    |     |
| V                         |        | 2   |     |     | 10  | 2   |     | 204 |     |      |     | 1   |     | 3   |      |     |
| W                         |        |     | 2   |     |     |     |     |     |     |      |     |     |     |     |      |     |
| X                         | 4      |     | 1   |     |     | 1   |     |     |     |      |     |     |     |     |      |     |
| Y                         | 9      |     | 151 | 210 |     |     | 1   |     |     |      |     | 1   | 1   |     |      |     |
| Z                         |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |     |
| -                         |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |     |
| unknown (?)               |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |     |
| not sequenced             |        |     |     |     |     |     |     |     |     |      |     |     |     |     |      |     |
| sum of seq <sup>2</sup>   | 212    | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212  | 212 | 212 | 212 | 212 | 212  | 212 |
| oomcaa <sup>3</sup>       | 51     | 97  | 151 | 210 | 174 | 160 | 193 | 204 | 199 | 212  | 201 | 207 | 189 | 208 | 211  |     |
| mcaa <sup>4</sup>         | N      | T   | Y   | Y   | A   | D   | S   | V   | K   | G    | R   | F   | T   | I   | S    |     |
| rel. oomcaa <sup>5</sup>  | 24%    | 46% | 71% | 99% | 82% | 75% | 91% | 96% | 94% | 100% | 95% | 98% | 89% | 98% | 100% |     |
| pos occupied <sup>6</sup> | 19     | 12  | 15  | 2   | 9   | 8   | 3   | 2   | 6   | 1    | 4   | 5   | 5   | 3   | 2    |     |

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Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|                           | 71            | 72  | 73  | 74  | 75  | 76  | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C    |
| A                         |               |     |     | 57  |     |     | 1   | 8   |     |     |     |     |     |     | 1    |
| B                         |               |     |     |     |     |     |     |     |     |     | 2   |     |     |     |      |
| C                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| D                         |               | 199 | 38  |     | 2   | 2   |     |     | 1   |     |     |     | 10  |     |      |
| E                         |               | 6   |     |     | 4   |     |     |     |     |     | 5   |     |     |     |      |
| F                         |               |     |     |     |     |     |     |     | 13  |     |     |     |     |     |      |
| G                         |               |     |     |     |     |     |     |     |     |     |     |     | 1   | 4   |      |
| H                         |               |     |     |     |     | 1   |     |     | 1   |     | 2   |     | 2   |     |      |
| I                         |               |     | 1   |     |     |     | 2   | 2   |     |     |     | 3   | 1   | 1   |      |
| K                         |               |     |     |     | 186 | 6   |     |     |     |     |     |     | 3   |     |      |
| L                         |               |     |     |     |     |     |     | 188 |     | 209 |     | 3   | 1   |     | 212  |
| M                         | 1             |     |     |     | 2   |     | 10  | 3   |     | 2   |     | 205 |     |     |      |
| N                         |               | 5   | 170 |     | 2   | 188 |     |     |     |     | 3   |     | 181 | 10  |      |
| P                         |               |     |     |     |     |     | 1   |     |     |     |     |     |     |     |      |
| Q                         |               |     |     |     | 7   |     |     |     |     |     | 199 |     |     |     |      |
| R                         | 211           |     |     |     | 1   | 1   |     |     |     |     |     |     | 2   | 8   |      |
| S                         |               |     |     | 153 | 8   | 10  | 56  |     | 3   |     |     |     | 6   | 186 |      |
| T                         |               |     |     |     |     |     | 142 |     |     |     | 1   |     | 4   | 2   |      |
| V                         |               |     |     | 1   |     |     |     | 11  |     | 1   |     | 1   |     |     |      |
| W                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| X                         |               | 2   | 2   |     |     | 4   |     |     |     |     |     |     | 1   |     |      |
| Y                         |               |     |     |     |     |     |     |     | 194 |     |     |     |     |     |      |
| Z                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| -                         |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| unknown (?)               |               |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
| not sequenced             |               |     | 1   | 1   |     |     |     |     |     |     |     |     |     |     |      |
| sum of seq <sup>2</sup>   | 212           | 212 | 211 | 211 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212  |
| oomcaa <sup>3</sup>       | 211           | 199 | 170 | 153 | 186 | 188 | 142 | 188 | 194 | 209 | 199 | 205 | 181 | 186 | 212  |
| mcaa <sup>4</sup>         | R             | D   | N   | S   | K   | N   | T   | L   | Y   | L   | Q   | M   | N   | S   | L    |
| rel. oomcaa <sup>5</sup>  | 100%          | 94% | 81% | 73% | 88% | 89% | 67% | 89% | 92% | 99% | 94% | 97% | 85% | 88% | 100% |
| pos occupied <sup>6</sup> | 2             | 4   | 4   | 3   | 8   | 7   | 6   | 5   | 5   | 3   | 6   | 4   | 11  | 7   | 1    |

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Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | 83  | 84  | 85  | 86  | 87  | 88  | 89  | 90   | 91  | 92   | 93  | 94  | 95  | 96  | 97  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|------|-----|------|-----|-----|-----|-----|-----|
| A                         |     | 149 | 1   |     | 1   | 207 |     |      |     |      | 173 | 2   | 15  | 9   | 11  |
| B                         |     |     |     |     |     |     |     |      |     |      |     |     |     |     |     |
| C                         |     |     |     |     |     |     |     |      | 1   | 210  |     | 5   | 2   |     | 1   |
| D                         |     | 5   | 15  | 209 |     |     |     |      |     |      |     | 2   | 54  | 7   | 6   |
| E                         | 1   |     | 190 |     |     |     |     |      |     |      |     |     | 11  | 2   | 11  |
| F                         |     |     |     |     |     |     | 1   |      | 15  |      |     | 1   |     | 9   | 6   |
| G                         | 1   | 1   | 6   |     |     | 4   | 1   |      |     |      | 2   | 8   | 34  | 26  | 35  |
| H                         |     | 1   |     |     |     |     |     |      | 1   |      |     |     |     | 3   | 11  |
| I                         |     | 8   |     |     |     |     | 2   |      |     |      |     |     | 4   | 15  | 10  |
| K                         | 30  |     |     |     |     |     |     |      |     |      |     | 60  | 4   | 3   | 5   |
| L                         |     |     |     |     |     |     | 18  |      |     |      |     | 1   | 6   | 11  | 7   |
| M                         |     |     |     |     | 2   |     | 1   |      |     |      |     |     |     | 6   | 1   |
| N                         |     | 1   |     | 1   |     |     |     |      |     |      |     | 2   | 20  | 4   | 3   |
| P                         |     | 9   |     |     |     |     |     |      |     |      | 1   | 3   | 4   | 29  | 10  |
| Q                         |     |     |     | 1   |     |     |     |      |     |      |     | 5   | 3   | 9   | 2   |
| R                         | 177 |     |     |     |     |     |     |      |     |      |     | 103 | 9   | 30  | 19  |
| S                         |     | 1   |     |     | 1   |     |     |      |     |      |     | 3   | 9   | 8   | 11  |
| T                         | 3   | 28  |     |     | 207 |     | 1   |      |     |      | 25  | 15  | 7   | 6   | 20  |
| V                         |     | 9   |     |     |     |     | 187 |      |     |      | 10  | 1   | 7   | 7   | 15  |
| W                         |     |     |     |     |     |     |     |      |     | 1    |     |     | 3   | 4   | 3   |
| X                         |     |     |     | 1   |     |     |     |      |     |      |     |     |     |     |     |
| Y                         |     |     |     |     |     |     |     | 211  | 194 |      |     |     | 12  | 9   | 8   |
| Z                         |     |     |     |     |     |     |     |      |     |      |     |     |     |     |     |
| -                         |     |     |     |     |     |     |     |      |     |      |     |     | 1   | 3   | 4   |
| unknown (?)               |     |     |     |     |     |     |     |      |     |      |     |     |     |     |     |
| not sequenced             |     |     |     |     | 1   | 1   | 1   | 1    | 1   | 1    | 1   | 1   | 1   | 7   | 12  |
| sum of seq <sup>2</sup>   | 212 | 212 | 212 | 212 | 211 | 211 | 211 | 211  | 211 | 211  | 211 | 211 | 205 | 200 | 199 |
| oomcaa <sup>3</sup>       | 177 | 149 | 190 | 209 | 207 | 207 | 187 | 211  | 194 | 210  | 173 | 103 | 54  | 30  | 35  |
| mcaa <sup>4</sup>         | R   | A   | E   | D   | T   | A   | V   | Y    | Y   | C    | A   | R   | D   | R   | G   |
| rel. oomcaa <sup>5</sup>  | 83% | 70% | 90% | 99% | 98% | 98% | 89% | 100% | 92% | 100% | 82% | 49% | 26% | 15% | 18% |
| pos occupied <sup>6</sup> | 5   | 10  | 4   | 4   | 4   | 2   | 7   | 1    | 4   | 2    | 5   | 14  | 18  | 20  | 21  |

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Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|                           | 98      | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   | 101 |  |
| A                         | 7       | 13  | 7   | 9   | 6   | 2   | 3   | 5   | 5   |     | 9   |     | 13  |     | 2   |  |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| C                         | 13      | 5   |     | 1   | 2   | 11  | 3   |     | 2   |     |     |     |     | 1   |     |  |
| D                         | 11      | 7   | 10  | 4   | 2   | 3   | 10  | 3   | 3   | 1   |     | 3   | 2   |     | 146 |  |
| E                         | 6       | 3   | 1   | 13  |     | 1   | 1   |     |     |     |     |     |     |     | 1   |  |
| F                         | 3       | 5   | 4   | 5   | 5   | 6   | 3   | 5   | 7   | 2   |     | 1   | 1   | 65  | 1   |  |
| G                         | 34      | 17  | 35  | 17  | 14  | 23  | 10  | 5   | 1   | 5   | 3   | 2   | 32  |     | 6   |  |
| H                         | 3       | 4   | 3   | 2   | 9   | 2   |     | 1   | 3   | 1   | 2   | 8   | 1   |     |     |  |
| I                         | 6       | 11  | 4   | 4   | 3   | 1   | 3   | 10  | 3   | 3   | 2   |     | 1   | 2   |     |  |
| K                         | 2       | 11  |     |     | 3   | 1   |     |     |     |     |     |     |     |     |     |  |
| L                         | 26      | 13  | 4   | 12  | 8   | 2   | 6   | 3   | 10  | 3   |     |     |     | 2   | 1   |  |
| M                         |         | 1   | 2   |     |     |     |     |     |     |     | 1   |     |     | 32  |     |  |
| N                         | 4       | 6   | 4   | 3   | 2   | 2   | 6   |     |     |     | 2   | 5   |     |     | 2   |  |
| P                         | 6       | 5   | 5   | 6   | 9   | 8   | 2   | 3   | 2   | 1   |     | 3   |     | 9   |     |  |
| Q                         | 4       |     | 1   | 1   | 1   | 1   | 1   |     |     |     |     | 1   |     |     |     |  |
| R                         | 4       | 10  | 9   | 7   | 5   | 5   | 2   | 3   | 1   |     | 1   |     | 2   |     | 4   |  |
| S                         | 16      | 28  | 27  | 25  | 24  | 8   | 11  | 9   | 3   |     | 2   | 3   | 1   | 1   | 1   |  |
| T                         | 6       | 12  | 9   | 17  | 17  | 1   | 2   | 5   | 1   | 9   | 3   | 1   |     |     |     |  |
| V                         | 13      | 7   | 15  | 4   | 3   | 6   | 2   | 12  |     | 1   | 1   | 1   | 1   |     |     |  |
| W                         | 6       | 5   | 6   | 7   | 2   | 4   |     |     |     | 1   |     | 6   | 10  |     |     |  |
| X                         |         |     |     | 1   |     |     |     |     |     |     |     |     |     |     | 1   |  |
| Y                         | 16      | 14  | 17  | 5   | 8   | 18  | 20  | 13  | 20  | 25  | 28  | 32  | 28  |     |     |  |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| -                         | 12      | 21  | 35  | 54  | 73  | 87  | 102 | 110 | 126 | 135 | 134 | 120 | 91  | 71  | 21  |  |
| unknown (?)               |         |     |     |     |     |     | 3   | 2   | 1   | 1   |     |     | 3   | 2   |     |  |
| not sequenced             | 14      | 14  | 14  | 14  | 15  | 19  | 21  | 22  | 23  | 23  | 23  | 25  | 25  | 26  | 25  |  |
| sum of seq <sup>2</sup>   | 198     | 198 | 198 | 197 | 196 | 192 | 190 | 189 | 188 | 188 | 188 | 186 | 186 | 185 | 186 |  |
| oomcaa <sup>3</sup>       | 34      | 28  | 35  | 54  | 73  | 87  | 102 | 110 | 126 | 135 | 134 | 120 | 91  | 71  | 146 |  |
| mcaa <sup>4</sup>         | G       | S   | G   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | D   |  |
| rel. oomcaa <sup>5</sup>  | 17%     | 14% | 18% | 27% | 37% | 45% | 54% | 58% | 67% | 72% | 71% | 65% | 49% | 38% | 78% |  |
| pos occupied <sup>6</sup> | 20      | 20  | 19  | 20  | 19  | 20  | 17  | 14  | 14  | 12  | 12  | 13  | 12  | 8   | 11  |  |

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Table 6D: Analysis of V heavy chain subgroup 3

| amino acid <sup>1</sup>   | Framework IV |     |     |     |     |     |     |     |     |     |     |     | sum  |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|                           | 102          | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 |      |
| A                         | 1            |     | 1   |     |     | 2   |     |     |     |     |     |     | 1767 |
| B                         |              |     |     | 1   |     |     |     |     |     |     |     |     | 13   |
| C                         |              |     |     |     |     |     |     |     |     |     |     |     | 470  |
| D                         | 2            |     |     |     |     |     |     |     |     |     |     |     | 1121 |
| E                         |              |     |     |     | 1   |     |     |     |     |     |     |     | 832  |
| F                         | 2            |     |     |     |     |     |     |     |     |     |     |     | 807  |
| G                         |              |     | 140 |     | 130 |     | 1   |     |     |     |     |     | 2743 |
| H                         | 4            |     |     |     |     |     |     |     |     |     |     |     | 179  |
| I                         | 15           |     |     |     |     |     |     |     | 1   | 1   |     |     | 651  |
| K                         |              |     |     | 13  |     |     |     |     |     |     |     |     | 933  |
| L                         | 10           |     |     | 1   |     |     | 91  |     |     |     |     | 2   | 1881 |
| M                         |              |     |     |     |     |     | 6   |     |     |     |     |     | 496  |
| N                         | 1            |     |     |     |     | 1   |     |     |     |     |     |     | 844  |
| P                         | 17           |     |     |     |     | 1   | 1   |     |     |     |     |     | 568  |
| Q                         |              |     |     | 111 |     |     |     |     |     |     |     |     | 949  |
| R                         |              |     |     | 8   |     |     |     |     |     |     |     |     | 1413 |
| S                         | 7            | 1   |     |     |     |     |     |     |     |     | 118 | 110 | 3009 |
| T                         |              |     |     |     |     | 123 | 27  |     | 122 |     |     | 1   | 1426 |
| V                         | 34           |     | 1   |     |     | 1   |     | 125 |     | 119 |     |     | 1851 |
| W                         |              | 158 |     |     |     |     |     |     |     |     |     |     | 686  |
| X                         |              |     |     |     |     |     |     |     |     |     |     |     | 26   |
| Y                         | 82           |     |     |     |     |     |     |     |     |     |     |     | 1598 |
| Z                         |              |     |     |     |     |     |     |     |     |     |     |     | 8    |
| -                         | 9            | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 1   | 1   | 2023 |
| unknown (?)               |              |     |     |     |     |     |     |     |     |     |     |     | 12   |
| not sequenced             | 27           | 50  | 67  | 75  | 78  | 81  | 83  | 84  | 86  | 89  | 92  | 97  | 1650 |
| sum of seq <sup>2</sup>   | 184          | 161 | 144 | 136 | 133 | 130 | 128 | 127 | 125 | 122 | 119 | 114 |      |
| oomcaa <sup>3</sup>       | 82           | 158 | 140 | 111 | 130 | 123 | 91  | 125 | 122 | 119 | 118 | 110 |      |
| mcaa <sup>4</sup>         | Y            | W   | G   | Q   | G   | T   | L   | V   | T   | V   | S   | S   |      |
| rel. oomcaa <sup>5</sup>  | 45%          | 98% | 97% | 82% | 98% | 95% | 71% | 98% | 98% | 98% | 99% | 96% |      |
| pos occupied <sup>6</sup> | 12           | 3   | 4   | 6   | 3   | 6   | 6   | 2   | 3   | 3   | 2   | 4   |      |

Table 6E: Analysis of V heavy chain subgroup 4

| amino acid <sup>1</sup>    | Framework I |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
|----------------------------|-------------|-----|-----|------|-----|-----|-----|------|-----|------|------|-----|------|-----|-----|-----|-----|------|-----|-----|
|                            | 1           | 2   | 3   | 4    | 5   | 6   | 7   | 8    | 9   | 10   | 11   | 12  | 13   | 14  | 15  | 16  | 17  | 18   | 19  | 20  |
| A                          |             |     |     |      |     |     |     |      | 19  |      |      |     |      | 1   |     |     | 1   |      | 1   |     |
| B                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| C                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| D                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| E                          |             |     |     |      | 32  |     |     |      |     |      |      |     |      |     |     | 44  |     |      |     |     |
| F                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| G                          |             |     |     |      |     |     |     | 54   | 1   | 53   |      |     |      |     |     | 2   |     |      |     |     |
| H                          |             |     | 4   |      | 2   |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| I                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| K                          |             |     |     |      |     |     |     |      |     |      |      | 1   | 54   |     |     |     |     |      | 1   |     |
| L                          |             | 7   |     | 54   |     |     |     |      |     | 53   | 19   |     |      | 1   |     |     |     | 53   |     | 50  |
| M                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| N                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| P                          |             |     |     |      |     |     |     |      | 33  |      |      |     |      | 51  | 1   |     |     |      |     | 2   |
| Q                          | 52          |     | 50  |      | 51  | 20  |     |      |     |      |      |     |      |     |     | 7   |     |      |     |     |
| R                          | 1           |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| S                          |             |     |     |      |     |     | 33  |      |     |      |      |     |      |     | 52  |     |     |      | 52  |     |
| T                          |             |     |     |      |     |     |     |      | 1   |      |      |     |      |     |     |     | 52  |      |     |     |
| V                          |             | 47  |     |      |     | 1   |     |      |     |      |      | 34  |      |     |     |     |     |      |     | 1   |
| W                          |             |     |     |      |     | 20  |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| X                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| Y                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| Z                          | 1           |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| -                          |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| unknown (?)                |             |     |     |      |     |     |     |      |     |      |      |     |      |     |     |     |     |      |     |     |
| not sequenced <sup>2</sup> | 3           | 3   | 3   | 3    | 4   | 4   | 4   | 3    | 3   | 4    | 4    | 3   | 3    | 4   | 4   | 4   | 4   | 4    | 3   | 4   |
| sum of seq <sup>3</sup>    | 54          | 54  | 54  | 54   | 53  | 53  | 53  | 54   | 54  | 53   | 53   | 54  | 54   | 53  | 53  | 53  | 53  | 53   | 54  | 53  |
| oomcaa <sup>4</sup>        | 52          | 47  | 50  | 54   | 51  | 32  | 33  | 54   | 33  | 53   | 53   | 34  | 54   | 51  | 52  | 44  | 52  | 53   | 52  | 50  |
| mcaa <sup>5</sup>          | Q           | V   | Q   | L    | Q   | E   | S   | G    | P   | G    | L    | V   | K    | P   | S   | E   | T   | L    | S   | L   |
| rel. oomcaa <sup>6</sup>   | 96%         | 87% | 93% | 100% | 96% | 60% | 62% | 100% | 61% | 100% | 100% | 63% | 100% | 96% | 98% | 83% | 98% | 100% | 96% | 94% |
| pos occupied <sup>6</sup>  | 3           | 2   | 2   | 1    | 2   | 3   | 2   | 1    | 4   | 1    | 1    | 3   | 1    | 3   | 2   | 3   | 2   | 1    | 3   | 3   |

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Table 6E: Analysis of V heavy chain subgroup 4

| amino acid <sup>1</sup>   |      |      |     |      |     |     |     |     |     |     | CDRI |     |     |     |     |      |     |      |     |      |
|---------------------------|------|------|-----|------|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|------|-----|------|
|                           | 21   | 22   | 23  | 24   | 25  | 26  | 27  | 28  | 29  | 30  | 31   | A   | B   | 32  | 33  | 34   | 35  | 36   | 37  | 38   |
| A                         |      |      | 22  |      |     |     |     |     |     |     |      |     |     | 1   |     |      |     |      |     |      |
| B                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| C                         |      | 53   |     |      |     |     |     |     |     |     |      |     |     |     | 1   |      |     |      |     |      |
| D                         |      |      | 1   |      |     |     |     |     |     |     | 4    | 1   | 1   | 1   |     |      | 1   |      |     |      |
| E                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| F                         |      |      |     |      | 1   |     |     |     | 22  |     |      |     |     | 1   | 1   |      |     |      | 1   |      |
| G                         |      |      |     |      |     | 53  | 53  |     |     |     | 21   | 3   | 4   |     |     |      | 8   |      |     |      |
| H                         |      |      |     |      |     |     | 1   |     |     |     |      |     |     | 2   |     |      |     |      |     |      |
| I                         |      |      | 1   |      |     |     |     | 1   | 32  |     |      |     |     |     |     |      |     |      | 51  |      |
| K                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| L                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      | 1   |      |
| M                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| N                         |      |      |     |      |     |     |     |     |     | 1   | 1    |     | 2   | 2   |     |      | 1   |      |     |      |
| P                         |      |      |     |      |     |     |     | 3   |     |     |      |     |     |     |     |      |     |      |     |      |
| Q                         |      |      |     |      |     |     |     |     |     |     | 1    |     |     |     |     |      |     |      |     |      |
| R                         |      |      |     |      |     | 1   |     |     |     | 3   | 2    |     | 1   |     |     |      |     |      |     | 57   |
| S                         |      |      | 2   |      | 35  |     |     | 51  | 1   | 52  | 25   | 5   | 9   | 1   |     |      | 44  |      | 1   |      |
| T                         | 53   |      | 29  |      |     |     |     |     |     |     | 2    | 1   |     |     |     |      | 3   |      |     |      |
| V                         |      |      |     | 55   |     | 1   |     |     | 1   |     |      |     |     |     |     |      |     |      | 3   |      |
| W                         |      |      |     |      |     |     |     |     |     |     |      | 1   |     |     | 2   | 56   |     | 57   |     |      |
| X                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| Y                         |      |      |     |      | 19  |     | 1   |     |     |     |      |     |     | 48  | 52  |      |     |      |     |      |
| Z                         |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| -                         |      |      |     |      |     |     |     |     |     |     |      | 45  | 39  |     |     |      |     |      |     |      |
| unknown (?)               |      |      |     |      |     |     |     |     |     |     |      |     |     |     |     |      |     |      |     |      |
| not sequenced             | 4    | 4    | 2   | 2    | 2   | 2   | 2   | 2   | 1   | 1   | 1    |     |     | 1   | 1   | 1    |     |      |     |      |
| sum of seq <sup>2</sup>   | 53   | 53   | 55  | 55   | 55  | 55  | 55  | 55  | 56  | 56  | 56   | 56  | 56  | 56  | 56  | 56   | 57  | 57   | 57  | 57   |
| oomcaa <sup>3</sup>       | 53   | 53   | 29  | 55   | 35  | 53  | 53  | 51  | 32  | 52  | 25   | 45  | 39  | 48  | 52  | 56   | 44  | 57   | 51  | 57   |
| mcaa <sup>4</sup>         | T    | C    | T   | V    | S   | G   | G   | S   | I   | S   | S    | -   | -   | Y   | Y   | W    | S   | W    | I   | R    |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 53% | 100% | 64% | 96% | 96% | 93% | 57% | 93% | 45%  | 80% | 70% | 86% | 93% | 100% | 77% | 100% | 89% | 100% |
| pos occupied <sup>6</sup> | 1    | 1    | 5   | 1    | 3   | 3   | 3   | 3   | 4   | 3   | 7    | 6   | 6   | 7   | 4   | 1    | 5   | 1    | 5   | 1    |

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Table 6E: Analysis of V heavy chain subgroup 4

|                           | Framework II |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
|---------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|-----|------|--|--|--|--|
| amino acid <sup>1</sup>   | 39           | 40  | 41  | 42  | 43  | 44  | 45  | 46  | 47  | 48  | 49  | 50  | 51  | 52  | A    | B    | C    | 53  | 54  | 55   |  |  |  |  |
| A                         |              |     | 8   | 1   |     |     |     |     |     |     | 1   |     |     |     |      |      |      |     |     |      |  |  |  |  |
| B                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| C                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| D                         |              |     |     |     |     |     |     |     |     |     |     |     |     | 1   |      |      |      | 1   |     |      |  |  |  |  |
| E                         |              |     |     | 1   |     |     |     | 56  |     |     |     | 22  |     |     |      |      |      |     |     |      |  |  |  |  |
| F                         |              |     |     |     |     |     |     |     |     |     |     | 1   |     | 1   |      |      |      |     |     |      |  |  |  |  |
| G                         |              |     |     | 55  |     | 55  |     |     |     |     | 56  | 1   |     |     |      |      |      | 1   |     | 57   |  |  |  |  |
| H                         |              | 2   |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 24  |     |      |  |  |  |  |
| I                         |              |     |     |     |     |     |     |     |     | 54  |     | 1   | 54  |     |      |      |      |     |     |      |  |  |  |  |
| K                         |              |     |     |     | 54  |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| L                         |              | 1   |     |     |     |     | 55  |     |     | 2   |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| M                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| N                         |              |     |     |     |     |     |     |     |     |     |     |     |     | 21  |      |      |      |     |     |      |  |  |  |  |
| P                         |              | 50  | 49  |     |     |     | 2   |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| Q                         | 56           |     |     |     |     |     |     | 1   |     |     |     | 1   |     |     |      |      |      |     |     |      |  |  |  |  |
| R                         |              |     |     |     | 3   | 2   |     |     |     |     |     | 9   |     | 1   |      |      |      |     |     |      |  |  |  |  |
| S                         |              | 3   |     |     |     |     |     |     |     |     |     | 7   |     | 1   |      |      |      |     |     | 52   |  |  |  |  |
| T                         | 1            | 1   |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      | 8   | 5   |      |  |  |  |  |
| V                         |              |     |     |     |     |     |     |     |     | 1   |     |     | 3   |     |      |      |      |     |     |      |  |  |  |  |
| W                         |              |     |     |     |     |     |     | 56  |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| X                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| Y                         |              |     |     |     |     |     |     |     | 1   |     |     | 15  |     | 32  |      |      |      | 23  |     |      |  |  |  |  |
| Z                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| -                         |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| unknown (?)               |              |     |     |     |     |     |     |     |     |     |     |     |     | 57  | 57   | 57   |      |     |     |      |  |  |  |  |
| not sequenced             |              |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |     |     |      |  |  |  |  |
| sum of seq <sup>2</sup>   | 57           | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57   | 57   | 57   | 57  | 57  | 57   |  |  |  |  |
| oomcaa <sup>3</sup>       | 56           | 50  | 49  | 55  | 54  | 55  | 55  | 56  | 56  | 54  | 56  | 22  | 54  | 32  | 57   | 57   | 57   | 24  | 52  | 57   |  |  |  |  |
| mcaa <sup>4</sup>         | Q            | P   | P   | G   | K   | G   | L   | E   | W   | I   | G   | E   | I   | Y   | -    | -    | -    | H   | S   | G    |  |  |  |  |
| rel. oomcaa <sup>5</sup>  | 98%          | 88% | 86% | 96% | 95% | 96% | 96% | 98% | 98% | 95% | 98% | 39% | 95% | 56% | 100% | 100% | 100% | 42% | 91% | 100% |  |  |  |  |
| pos occupied <sup>6</sup> | 2            | 5   | 2   | 3   | 2   | 2   | 2   | 2   | 2   | 3   | 2   | 8   | 2   | 6   | 1    | 1    | 1    | 5   | 2   | 1    |  |  |  |  |

Table 6E: Analysis of V heavy chain subgroup 4

|                           | CDR II |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
|---------------------------|--------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|--|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61  | 62   | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72  | 73  | 74   | 75  |  |
| A                         |        | 1   |     |     |     |     |      |     |     |     | 1   |     | 1   |     |     | 1   |     |     |      | 1   |  |
| B                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| C                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| D                         |        |     | 2   |     |     |     |      |     |     |     |     | 1   |     |     |     |     | 55  |     |      |     |  |
| E                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     | 1   |     |      |     |  |
| F                         |        |     |     | 3   |     |     |      |     |     |     |     |     |     |     |     |     |     | 1   |      |     |  |
| G                         | 1      |     |     |     |     |     |      |     |     | 1   |     |     |     |     |     |     |     |     |      |     |  |
| H                         |        |     | 2   |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| I                         | 1      | 1   |     |     |     |     |      |     |     |     |     | 1   | 1   | 48  |     | 3   |     |     |      |     |  |
| K                         |        |     |     |     | 1   |     |      |     | 53  |     |     |     |     |     |     |     |     | 1   |      | 51  |  |
| L                         |        |     |     |     |     | 1   |      | 55  |     |     |     | 1   |     |     |     | 3   |     |     |      | 1   |  |
| M                         |        |     |     |     |     |     |      |     |     |     |     |     |     | 7   |     |     |     | 2   |      |     |  |
| N                         | 2      |     | 40  |     | 53  |     |      |     |     |     |     |     |     | 2   |     |     |     |     |      | 1   |  |
| P                         |        |     |     |     |     | 54  |      | 1   |     |     |     |     |     |     |     |     |     |     |      |     |  |
| Q                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     | 1   |     |      |     |  |
| R                         | 2      |     |     |     |     |     |      |     | 3   |     | 56  |     |     |     |     |     |     |     |      | 2   |  |
| S                         | 49     |     | 1   |     | 2   |     | 56   |     |     | 56  |     |     | 1   |     | 56  |     |     | 1   | 57   |     |  |
| T                         | 1      | 54  | 1   |     |     | 1   |      |     | 1   |     |     |     | 51  |     | 1   |     |     | 52  |      |     |  |
| V                         | 1      | 1   |     |     |     |     |      |     |     |     |     | 53  |     | 2   |     | 50  |     |     |      | 1   |  |
| W                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| X                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| Y                         |        |     | 11  | 54  |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| Z                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| -                         |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| unknown (?)               |        |     |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |      |     |  |
| not sequenced             |        |     |     |     | 1   | 1   | 1    | 1   |     |     |     | 1   | 1   |     |     |     |     |     |      |     |  |
| sum of seq <sup>2</sup>   | 57     | 57  | 57  | 57  | 56  | 56  | 56   | 56  | 57  | 57  | 57  | 56  | 56  | 57  | 57  | 57  | 57  | 57  | 57   | 57  |  |
| oomcaa <sup>3</sup>       | 49     | 54  | 40  | 54  | 53  | 54  | 56   | 55  | 53  | 56  | 56  | 53  | 51  | 48  | 56  | 50  | 55  | 52  | 57   | 51  |  |
| mcaa <sup>4</sup>         | S      | T   | N   | Y   | N   | P   | S    | L   | K   | S   | R   | V   | T   | I   | S   | V   | D   | T   | S    | K   |  |
| rel. oomcaa <sup>5</sup>  | 86%    | 95% | 70% | 95% | 95% | 96% | 100% | 98% | 93% | 98% | 98% | 95% | 91% | 84% | 98% | 88% | 96% | 91% | 100% | 89% |  |
| pos occupied <sup>6</sup> | 7      | 4   | 6   | 2   | 3   | 3   | 1    | 2   | 3   | 2   | 2   | 4   | 5   | 3   | 2   | 4   | 3   | 5   | 1    | 6   |  |

Table 6E: Analysis of V heavy chain subgroup 4

| Framework III             |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
|---------------------------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|-----|------|-----|------|-----|------|
| amino acid <sup>1</sup>   | 76  | 77  | 78  | 79   | 80  | 81  | 82  | A   | B   | C   | 83  | 84  | 85   | 86   | 87  | 88   | 89  | 90   | 91  | 92   |
| A                         |     |     |     |      |     |     |     |     |     |     |     | 55  | 57   |      |     | 57   |     |      |     |      |
| B                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| C                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     | 57   |
| D                         |     |     |     |      | 1   |     |     |     |     |     |     |     |      | 57   |     |      |     |      |     |      |
| E                         |     |     |     |      |     | 1   |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| F                         |     |     | 54  |      |     |     |     |     | 1   |     |     |     |      |      |     |      |     |      |     |      |
| G                         |     |     |     |      |     |     |     | 1   |     |     |     |     |      |      |     |      |     |      |     |      |
| H                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| I                         |     |     | 1   |      |     |     |     | 1   |     |     | 3   |     |      |      |     |      |     |      |     |      |
| K                         | 3   |     |     |      |     | 46  |     | 2   |     |     |     |     |      |      |     |      |     |      |     |      |
| L                         |     | 3   | 1   |      | 55  |     | 53  |     |     | 2   |     |     |      |      |     |      | 1   |      |     |      |
| M                         |     |     |     |      |     | 1   | 1   |     |     | 1   |     |     |      |      |     |      | 1   |      |     |      |
| N                         | 54  |     |     |      |     | 3   |     | 3   | 1   |     |     |     |      |      |     |      |     |      |     |      |
| P                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| Q                         |     | 54  |     |      | 1   | 1   |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| R                         |     |     |     |      |     | 2   |     | 2   |     |     |     | 1   |      |      |     |      |     |      |     |      |
| S                         |     |     | 1   | 57   |     | 2   | 1   | 44  | 55  |     | 1   |     |      |      | 2   |      |     |      | 1   |      |
| T                         |     |     |     |      |     | 1   |     | 4   |     |     | 53  |     |      |      | 55  |      |     |      |     |      |
| V                         |     |     |     |      |     |     | 2   |     |     | 54  |     | 1   |      |      |     |      | 55  |      |     |      |
| W                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| X                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| Y                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| Z                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     | 57   | 56  |      |
| -                         |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| unknown (?)               |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| not sequenced             |     |     |     |      |     |     |     |     |     |     |     |     |      |      |     |      |     |      |     |      |
| sum of seq <sup>2</sup>   | 57  | 57  | 57  | 57   | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57  | 57   | 57   | 57  | 57   | 57  | 57   | 57  | 57   |
| oomcaa <sup>3</sup>       | 54  | 54  | 54  | 57   | 55  | 46  | 53  | 44  | 55  | 54  | 53  | 55  | 57   | 57   | 55  | 57   | 55  | 57   | 56  | 57   |
| mcaa <sup>4</sup>         | N   | Q   | F   | S    | L   | K   | L   | S   | S   | V   | T   | A   | A    | D    | T   | A    | V   | Y    | Y   | C    |
| rel. oomcaa <sup>5</sup>  | 95% | 95% | 95% | 100% | 96% | 81% | 93% | 77% | 96% | 95% | 93% | 96% | 100% | 100% | 96% | 100% | 96% | 100% | 98% | 100% |
| pos occupied <sup>6</sup> | 2   | 2   | 4   | 1    | 3   | 8   | 4   | 7   | 3   | 3   | 3   | 3   | 1    | 1    | 2   | 1    | 3   | 1    | 2   | 1    |

176

Table 6E: Analysis of V heavy chain subgroup 4

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 101 |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 93      | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   |     |
| A                         | 56      |     | 3   | 3   | 3   | 2   | 5   | 4   | 2   | 2   | 4   |     | 2   | 1   |     | 1   | 1   | 12  |     |     |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |         |     |     |     | 1   |     |     |     | 1   |     |     |     |     |     |     |     |     |     |     |     |
| D                         |         |     | 6   |     | 5   | 5   | 5   | 4   | 3   | 2   | 4   | 3   | 1   |     | 1   | 2   | 1   |     |     | 41  |
| E                         |         |     | 6   | 1   | 1   | 2   | 1   |     |     | 1   | 3   | 1   | 2   | 1   |     |     |     |     |     |     |
| F                         |         |     |     | 4   | 1   | 1   |     | 2   | 3   | 2   | 2   |     | 1   | 1   |     |     |     |     | 31  |     |
| G                         |         |     | 25  | 9   | 10  | 8   | 10  | 11  | 4   | 7   | 7   | 6   | 1   | 1   | 1   | 2   | 1   | 9   |     |     |
| H                         |         |     | 1   |     |     |     | 1   |     |     |     |     |     | 1   |     |     | 1   |     |     |     | 2   |
| I                         |         |     |     | 1   |     | 2   | 4   | 1   | 3   | 2   | 3   |     | 1   |     |     |     |     |     | 1   |     |
| K                         |         |     | 2   | 1   |     |     |     |     |     | 2   | 2   |     |     | 1   |     |     |     |     |     |     |
| L                         |         |     | 2   | 6   | 7   | 3   | 5   | 3   | 2   | 4   | 1   | 5   | 3   | 3   |     | 1   |     |     |     |     |
| M                         |         |     |     | 1   | 4   |     | 3   | 1   |     | 2   | 1   |     |     |     |     |     |     |     | 9   |     |
| N                         |         |     |     | 3   |     |     |     |     | 2   | 1   | 1   | 5   | 1   | 1   |     |     | 2   |     |     |     |
| P                         |         |     |     | 4   | 5   | 3   | 1   | 1   | 2   | 1   | 1   | 1   | 2   | 3   | 1   | 2   | 1   |     |     |     |
| Q                         |         |     |     |     | 1   | 1   |     | 1   |     |     | 1   | 1   |     |     | 3   |     |     |     | 1   |     |
| R                         |         | 54  | 4   | 12  | 2   | 5   | 5   | 3   | 2   | 3   | 1   | 2   |     |     | 2   | 1   |     |     |     |     |
| S                         |         | 1   | 1   | 4   | 8   | 8   | 1   | 2   | 5   | 7   | 4   | 2   | 1   | 1   | 1   |     |     |     |     |     |
| T                         |         | 1   | 1   | 2   | 1   | 3   | 4   | 4   | 3   | 3   |     |     | 1   | 1   | 1   |     |     |     |     |     |
| V                         | 1       | 1   | 4   | 2   | 2   | 5   | 4   | 4   | 7   | 3   | 1   | 2   | 1   |     |     |     |     |     |     |     |
| W                         |         |     | 1   | 2   | 1   | 2   | 2   | 4   | 5   | 1   | 1   | 2   |     | 2   | 1   |     | 3   | 2   |     |     |
| X                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |         |     |     | 1   | 4   | 5   | 3   | 6   | 4   | 2   | 3   | 4   | 8   | 4   | 8   | 3   | 5   | 8   |     | 2   |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |         |     |     |     |     | 1   | 2   | 4   | 6   | 9   | 11  | 16  | 23  | 27  | 29  | 34  | 31  | 14  | 4   |     |
| unknown (?)               |         |     |     |     |     |     |     |     |     |     |     |     |     | 1   |     |     | 1   | 1   | 1   |     |
| not sequenced             |         |     | 1   | 1   | 1   | 1   | 1   | 2   | 3   | 3   | 6   | 7   | 8   | 9   | 9   | 10  | 11  | 11  | 11  | 11  |
| sum of seq <sup>2</sup>   | 57      | 57  | 56  | 56  | 56  | 56  | 56  | 55  | 54  | 54  | 51  | 50  | 49  | 48  | 48  | 47  | 46  | 46  | 46  | 46  |
| oomcaa <sup>1</sup>       | 56      | 54  | 25  | 12  | 10  | 8   | 10  | 11  | 7   | 9   | 11  | 16  | 23  | 27  | 29  | 34  | 31  | 14  | 31  | 41  |
| mcaa <sup>1</sup>         | A       | R   | G   | R   | G   | G   | G   | G   | V   | -   | -   | -   | -   | -   | -   | -   | -   | -   | F   | D   |
| rel. oomcaa <sup>5</sup>  | 98%     | 95% | 45% | 21% | 18% | 14% | 18% | 20% | 13% | 17% | 22% | 32% | 47% | 56% | 60% | 72% | 67% | 30% | 67% | 89% |
| pos occupied <sup>6</sup> | 2       | 4   | 12  | 16  | 16  | 16  | 16  | 16  | 16  | 18  | 18  | 13  | 15  | 13  | 10  | 9   | 8   | 5   | 4   | 4   |

Table 6E: Analysis of V heavy chain subgroup 4

| amino acid <sup>1</sup>   | Framework IV |      |      |     |      |     |     |      |     |      |      |     | sum |
|---------------------------|--------------|------|------|-----|------|-----|-----|------|-----|------|------|-----|-----|
|                           | 102          | 103  | 104  | 105 | 106  | 107 | 108 | 109  | 110 | 111  | 112  | 113 |     |
| A                         |              |      |      |     |      | 1   |     |      | 1   |      |      |     | 332 |
| B                         |              |      |      |     |      |     |     |      |     |      |      |     |     |
| C                         |              |      |      |     |      |     |     |      |     |      |      |     | 113 |
| D                         |              |      |      |     |      |     |     |      |     |      |      |     | 210 |
| E                         |              |      |      |     |      |     |     |      |     |      |      |     | 176 |
| F                         |              |      |      |     |      |     |     |      |     |      |      |     | 135 |
| G                         |              |      | 41   |     | 40   | 1   |     |      |     |      |      |     | 674 |
| H                         | 1            |      |      |     |      |     |     |      | 1   |      |      |     | 45  |
| I                         | 9            |      |      |     |      | 1   |     |      |     |      |      |     | 282 |
| K                         |              |      |      | 3   |      |     |     |      |     |      |      |     | 278 |
| L                         | 4            |      |      |     |      |     | 19  |      |     |      |      |     | 540 |
| M                         |              |      |      |     |      |     | 9   |      |     |      |      |     | 43  |
| N                         |              |      |      |     |      | 1   |     |      |     |      |      |     | 204 |
| P                         | 3            |      |      | 2   |      |     |     |      |     |      |      | 2   | 281 |
| Q                         |              |      |      | 29  |      |     |     |      |     |      |      |     | 334 |
| R                         | 1            |      |      | 4   |      |     | 1   |      |     |      |      |     | 250 |
| S                         | 1            |      |      | 1   |      |     |     |      |     |      | 36   | 33  | 986 |
| T                         |              |      |      | 1   |      | 33  | 8   |      | 34  |      |      |     | 532 |
| V                         | 12           |      |      |     |      |     |     | 36   |     | 36   |      |     | 488 |
| W                         |              | 46   |      |     |      |     |     |      |     |      |      |     | 267 |
| X                         |              |      |      |     |      |     |     |      |     |      |      |     |     |
| Y                         | 16           |      |      |     |      |     |     |      |     |      |      |     | 455 |
| Z                         |              |      |      |     |      |     |     |      |     |      |      |     | 1   |
| -                         |              |      |      |     |      |     |     |      |     |      |      |     | 466 |
| unknown (?)               |              |      |      |     |      |     |     |      |     |      |      |     | 4   |
| not sequenced             | 10           | 11   | 16   | 17  | 17   | 20  | 20  | 21   | 21  | 21   | 21   | 22  | 426 |
| sum of seq <sup>2</sup>   | 47           | 46   | 41   | 40  | 40   | 37  | 37  | 36   | 36  | 36   | 36   | 35  |     |
| oomcaa <sup>1</sup>       | 16           | 46   | 41   | 29  | 40   | 33  | 19  | 36   | 34  | 36   | 36   | 33  |     |
| mcaa <sup>4</sup>         | Y            | W    | G    | Q   | G    | T   | L   | V    | T   | V    | S    | S   |     |
| rel. oomcaa <sup>5</sup>  | 34%          | 100% | 100% | 73% | 100% | 89% | 51% | 100% | 94% | 100% | 100% | 94% |     |
| pos occupied <sup>6</sup> | 8            | 1    | 1    | 6   | 1    | 5   | 4   | 1    | 3   | 1    | 1    | 2   |     |



Table 6F: Analysis of V heavy chain subgroup 5

| amino acid <sup>1</sup>   | Framework I |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
|---------------------------|-------------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|------|
|                           | 1           | 2   | 3    | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18   | 19  | 20   |
| A                         |             |     |      |     | 1   |     |     | 1   | 89  |     | 1   |     |     | 1   |     |     |     |      |     |      |
| B                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| C                         |             |     |      |     |     |     | 1   |     |     |     |     |     |     |     |     |     |     |      |     |      |
| D                         |             |     |      |     |     |     |     |     |     | 2   |     |     |     |     |     |     |     |      |     |      |
| E                         | 88          | 1   |      |     | 2   |     |     |     | 4   | 93  |     |     |     |     |     | 92  |     |      |     |      |
| F                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     | 1   |      |     |      |
| G                         | 1           |     |      |     |     |     |     | 92  |     |     |     |     |     |     | 94  |     |     |      |     |      |
| H                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| I                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     | 96   |
| K                         |             |     |      |     |     |     |     |     |     |     |     | 94  | 94  |     |     |     |     |      | 77  |      |
| L                         |             | 1   |      | 91  |     | 2   |     |     |     |     |     |     |     |     |     |     |     | 95   |     |      |
| M                         |             |     |      |     |     |     |     |     |     |     | 3   |     |     |     |     |     |     |      | 1   |      |
| N                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| P                         |             |     |      | 1   |     |     |     |     | 1   |     |     |     |     | 94  |     |     |     |      |     |      |
| Q                         | 3           |     | 92   |     | 1   | 90  |     |     |     |     |     |     |     |     |     | 3   |     |      | 1   |      |
| R                         |             |     |      |     |     | 1   |     |     |     |     |     | 1   | 1   |     | 1   |     |     |      | 17  |      |
| S                         |             |     |      |     |     |     | 92  |     |     |     |     |     |     |     |     |     | 94  |      |     |      |
| T                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| V                         |             | 90  |      |     | 89  |     |     |     | 1   |     | 91  |     |     |     |     |     |     |      |     |      |
| W                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| X                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| Y                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| Z                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| -                         |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| unknown (?)               |             |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |      |
| not sequenced             | 5           | 5   | 5    | 5   | 4   | 4   | 4   | 4   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2    | 1   | 1    |
| sum of seq <sup>2</sup>   | 92          | 92  | 92   | 92  | 93  | 93  | 93  | 93  | 95  | 95  | 95  | 95  | 95  | 95  | 95  | 95  | 95  | 95   | 96  | 96   |
| oomcaa <sup>3</sup>       | 88          | 90  | 92   | 91  | 89  | 90  | 92  | 92  | 89  | 93  | 91  | 94  | 94  | 94  | 94  | 92  | 94  | 95   | 77  | 96   |
| mcaa <sup>4</sup>         | E           | V   | Q    | L   | V   | Q   | S   | G   | A   | E   | V   | K   | K   | P   | G   | E   | S   | L    | K   | I    |
| rel. oomcaa <sup>5</sup>  | 96%         | 98% | 100% | 99% | 96% | 97% | 99% | 99% | 94% | 98% | 96% | 99% | 99% | 99% | 99% | 97% | 99% | 100% | 80% | 100% |
| pos occupied <sup>6</sup> | 3           | 3   | 1    | 2   | 4   | 3   | 2   | 2   | 4   | 2   | 3   | 2   | 2   | 2   | 2   | 2   | 2   | 1    | 4   | 1    |

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**Table 6F: Analysis of V heavy chain subgroup 5**

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Table 6F: Analysis of V heavy chain subgroup 5

| amino acid <sup>1</sup>   | Framework II |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
|---------------------------|--------------|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|----|----|----|----|
|                           | 39           | 40  | 41  | 42   | 43  | 44  | 45  | 46   | 47  | 48  | 49  | 50  | 51  | 52  | A   | B    | C    | 53  | 54  | 55  |    |    |    |    |
| A                         |              |     | 1   |      |     | 1   |     |      |     |     |     |     |     |     | 1   |      |      | 2   | 1   |     |    |    |    |    |
| B                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| C                         |              |     |     |      |     |     |     |      |     |     |     |     |     | 1   |     |      |      | 1   |     |     |    |    |    |    |
| D                         |              |     |     |      |     |     |     |      |     |     |     |     |     | 14  |     |      |      | 8   | 93  |     |    |    |    |    |
| E                         |              |     |     | 3    |     |     | 97  |      |     |     |     |     |     |     |     |      |      |     | 2   |     |    |    |    |    |
| F                         |              |     |     |      |     |     |     |      |     |     |     | 1   |     | 2   |     |      |      |     |     |     |    |    |    |    |
| G                         |              |     | 97  |      | 96  |     |     |      |     |     | 95  |     |     |     |     |      |      | 69  | 1   |     |    |    |    |    |
| H                         |              |     |     |      |     |     |     |      |     |     |     |     |     | 3   | 1   |      |      |     |     |     |    |    |    |    |
| I                         |              |     |     |      |     |     |     |      |     | 1   |     | 75  | 92  |     |     |      |      |     |     |     |    |    |    |    |
| K                         |              | 1   |     |      | 94  |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| L                         |              |     |     |      |     | 94  |     |      | 2   |     | 2   | 1   |     |     |     |      |      |     |     |     |    |    |    |    |
| M                         |              | 92  |     |      |     |     |     |      | 89  |     |     |     | 1   |     |     |      |      |     |     |     |    |    |    |    |
| N                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| P                         |              |     | 96  |      |     |     | 2   |      |     |     |     |     |     | 1   | 93  |      |      |     |     | 1   |    |    |    |    |
| Q                         | 97           |     |     |      |     |     | 1   |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| R                         |              | 1   |     |      |     |     |     |      |     |     | 1   | 14  |     |     |     |      |      |     | 1   |     |    |    |    |    |
| S                         |              |     |     |      |     |     |     |      |     |     |     | 1   |     |     | 1   |      |      | 16  |     | 96  |    |    |    |    |
| T                         |              | 1   |     |      |     |     |     |      |     |     |     | 3   | 1   |     | 1   |      |      |     |     |     |    |    |    |    |
| V                         |              | 2   |     |      |     |     |     |      |     | 5   | 1   | 1   | 2   |     |     |      |      |     |     |     |    |    |    |    |
| W                         |              |     |     |      |     |     |     | 94   |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| X                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| Y                         |              |     |     |      |     |     |     |      | 3   |     |     |     |     | 76  |     |      |      |     |     |     |    |    |    |    |
| Z                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| -                         |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      | 97   | 97  |     |     |    |    |    |    |
| unknown (?)               |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| not sequenced             |              |     |     |      |     |     |     |      |     |     |     |     |     |     |     |      |      |     |     |     |    |    |    |    |
| sum of seq <sup>2</sup>   | 97           | 97  | 97  | 97   | 97  | 97  | 97  | 97   | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97   | 97   | 97  | 97  | 97  | 97 | 97 | 97 | 97 |
| oomcaa <sup>1</sup>       | 97           | 92  | 96  | 97   | 94  | 96  | 94  | 97   | 94  | 89  | 95  | 75  | 92  | 76  | 93  | 97   | 97   | 69  | 93  | 96  |    |    |    |    |
| mcaa <sup>4</sup>         | Q            | M   | P   | G    | K   | G   | L   | E    | W   | M   | G   | I   | I   | Y   | P   | -    | -    | G   | D   | S   |    |    |    |    |
| rel. oomcaa <sup>5</sup>  | 100%         | 95% | 99% | 100% | 97% | 99% | 97% | 100% | 97% | 92% | 98% | 77% | 95% | 78% | 96% | 100% | 100% | 71% | 96% | 99% |    |    |    |    |
| pos occupied <sup>6</sup> | 1            | 5   | 2   | 1    | 2   | 2   | 3   | 1    | 2   | 4   | 3   | 7   | 5   | 6   | 5   | 1    | 1    | 6   | 4   | 2   |    |    |    |    |

Table 6F: Analysis of V heavy chain subgroup 5

| CDR II                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|--|--|--|--|--|
| amino acid <sup>a</sup>   | 56  | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72   | 73  | 74  | 75  |  |  |  |  |  |
| A                         |     | 6   |     |     |     |     | 1   |     |     |     |     |     |     |     |     | 88  |      |     |     |     |  |  |  |  |  |
| B                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| C                         |     |     |     |     | 1   |     |     |     |     | 1   |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| D                         | 77  |     |     |     |     |     |     |     |     | 2   |     |     |     |     |     |     | 97   |     |     |     |  |  |  |  |  |
| E                         | 3   |     |     |     |     |     |     |     | 2   |     |     |     |     |     |     |     |      | 2   |     |     |  |  |  |  |  |
| F                         |     |     |     | 2   |     |     |     | 91  |     |     |     | 1   |     | 3   |     |     |      |     |     |     |  |  |  |  |  |
| G                         | 1   |     |     |     |     |     |     |     | 94  |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| H                         |     |     |     |     |     |     |     |     |     | 15  |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| I                         |     | 4   | 1   |     |     |     |     | 1   |     |     |     | 3   |     | 88  |     |     |      |     |     | 91  |  |  |  |  |  |
| K                         |     |     | 2   |     |     |     |     |     |     |     |     |     |     |     |     |     |      | 93  |     |     |  |  |  |  |  |
| L                         |     |     |     |     |     | 1   |     | 4   |     |     |     |     |     |     | 2   |     |      |     |     |     |  |  |  |  |  |
| M                         |     |     |     |     |     |     |     |     |     |     |     |     |     | 3   |     |     |      |     |     | 1   |  |  |  |  |  |
| N                         | 2   |     | 14  | 2   |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| P                         |     |     |     |     |     | 95  | 1   |     | 1   |     |     |     |     |     |     |     |      |     | 1   |     |  |  |  |  |  |
| Q                         |     |     |     |     |     |     |     |     | 91  | 81  |     |     |     |     |     |     |      | 1   |     |     |  |  |  |  |  |
| R                         |     |     | 78  |     |     |     |     |     | 3   | 1   |     |     |     | 1   |     |     |      | 1   |     |     |  |  |  |  |  |
| S                         | 2   | 2   |     |     | 95  | 1   | 95  | 1   |     |     |     |     | 1   |     | 95  |     |      |     | 96  | 1   |  |  |  |  |  |
| T                         |     | 85  | 2   |     | 1   |     |     |     |     |     |     |     | 96  |     |     |     |      |     |     | 4   |  |  |  |  |  |
| V                         |     |     |     | 1   |     |     |     |     |     |     | 93  |     | 2   |     | 9   |     |      |     |     |     |  |  |  |  |  |
| W                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| Y                         | 12  |     |     | 92  |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| Z                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| -                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| not sequenced             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |     |     |     |  |  |  |  |  |
| sum of seq <sup>b</sup>   | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97   | 97  | 97  | 97  |  |  |  |  |  |
| oomcaa <sup>c</sup>       | 77  | 85  | 78  | 92  | 95  | 95  | 95  | 91  | 91  | 94  | 81  | 93  | 96  | 88  | 95  | 88  | 97   | 93  | 96  | 91  |  |  |  |  |  |
| mcaa <sup>d</sup>         | D   | T   | R   | Y   | S   | P   | S   | F   | Q   | G   | Q   | V   | T   | I   | S   | A   | D    | K   | S   | I   |  |  |  |  |  |
| rel. oomcaa <sup>e</sup>  | 79% | 88% | 80% | 95% | 98% | 98% | 98% | 94% | 94% | 97% | 84% | 96% | 99% | 91% | 98% | 91% | 100% | 96% | 99% | 94% |  |  |  |  |  |
| pos occupied <sup>f</sup> | 6   | 4   | 5   | 4   | 3   | 3   | 3   | 4   | 4   | 3   | 3   | 3   | 2   | 5   | 2   | 2   | 1    | 4   | 2   | 4   |  |  |  |  |  |

Table 6F: Analysis of V heavy chain subgroup 5

| amino acid <sup>1</sup>   | Framework III |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |       |
|---------------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-------|
|                           | 76            | 77  | 78  | 79  | 80  | 81  | 82  | A   | B   | C    | 83  | 84  | 85  | 86  | 87  | 88  | 89    |
| A                         |               | 1   | 91  |     |     |     |     |     |     |      | 1   | 96  |     |     |     | 93  |       |
| B                         |               |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |       |
| C                         |               |     |     |     |     |     | 1   |     |     |      |     |     |     |     |     |     | 95    |
| D                         |               |     |     | 1   |     |     |     |     |     |      |     |     |     | 96  |     |     |       |
| E                         |               |     |     |     |     | 1   |     |     |     |      | 1   |     |     |     |     |     |       |
| F                         |               |     |     | 1   |     |     |     |     |     |      |     |     |     |     |     |     | 2 6   |
| G                         |               |     |     |     |     |     |     | 3   | 1   |      |     |     |     |     |     | 4   |       |
| H                         |               |     |     |     |     | 3   |     |     |     |      |     |     |     |     |     |     |       |
| I                         |               |     |     |     |     |     |     |     |     |      |     |     |     |     | 2   |     | 9     |
| K                         |               |     |     |     |     |     |     |     |     |      | 91  |     |     |     |     |     | 1     |
| L                         |               |     |     |     | 96  |     |     |     |     | 97   |     |     |     |     |     |     | 2     |
| M                         |               |     |     |     |     |     |     |     |     |      |     |     |     |     |     | 84  |       |
| N                         | 7             |     |     |     |     |     |     | 2   | 2   |      |     |     |     |     | 2   |     |       |
| P                         |               |     | 1   |     |     |     |     |     |     |      |     |     |     |     |     |     |       |
| Q                         |               |     |     |     |     | 93  |     |     |     |      |     |     |     |     |     |     |       |
| R                         | 1             |     |     |     |     |     | 1   | 1   | 3   |      | 3   |     |     |     |     |     |       |
| S                         | 87            | 2   | 1   | 1   |     |     |     | 90  | 91  |      |     |     | 96  |     | 5   |     |       |
| T                         | 2             | 94  | 2   |     |     |     |     | 1   |     |      | 1   | 1   | 1   |     | 88  |     | 1     |
| V                         |               |     | 2   |     | 1   |     |     |     |     |      |     |     |     | 1   |     |     |       |
| W                         |               |     |     |     |     |     | 95  |     |     |      |     |     |     |     |     |     |       |
| X                         |               |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |       |
| Y                         |               |     |     | 94  |     |     |     |     |     |      |     |     |     |     |     |     | 94 89 |
| Z                         |               |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |       |
| -                         |               |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |       |
| unknown (?)               |               |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     |       |
| not sequenced             |               |     |     |     |     |     |     |     |     |      |     |     |     |     |     |     | 1 2 2 |
| sum of seq <sup>2</sup>   | 97            | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97  | 97   | 97  | 97  | 97  | 97  | 97  | 97  | 96    |
| oomcaa <sup>3</sup>       | 87            | 94  | 91  | 94  | 96  | 93  | 95  | 90  | 91  | 97   | 91  | 96  | 96  | 96  | 88  | 93  | 84    |
| mcaa <sup>4</sup>         | S             | T   | A   | Y   | L   | Q   | W   | S   | S   | L    | K   | A   | S   | D   | T   | A   | M     |
| rel. oomcaa <sup>5</sup>  | 90%           | 97% | 94% | 97% | 99% | 96% | 98% | 93% | 94% | 100% | 94% | 99% | 99% | 99% | 91% | 96% | 87%   |
| pos occupied <sup>6</sup> | 4             | 3   | 5   | 4   | 2   | 3   | 3   | 5   | 4   | 1    | 5   | 2   | 2   | 2   | 4   | 2   | 5     |

Table 6F: Analysis of V heavy chain subgroup 5

| amino acid <sup>1</sup>   | CDR III |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                           | 93      | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   |
| A                         | 92      |     | 1   | 1   | 2   |     | 3   | 4   | 3   | 2   |     | 1   |     |     | 1   |     |     | 4   | 2   |
| B                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |         |     |     |     |     | 1   | 1   | 1   |     |     | 2   |     | 1   |     |     |     |     |     |     |
| D                         |         |     |     | 3   | 3   | 3   | 3   | 1   | 2   | 1   | 1   | 2   |     | 2   | 1   | 1   | 2   |     | 37  |
| E                         |         |     | 1   | 1   | 1   | 2   |     |     | 1   | 1   |     |     |     | 1   |     |     | 1   |     |     |
| F                         |         |     |     |     | 1   |     | 3   |     |     | 3   | 2   |     | 1   |     |     |     |     |     | 26  |
| G                         |         |     | 1   | 9   | 11  | 12  | 12  | 5   | 2   | 4   | 3   | 10  | 2   | 1   |     |     |     | 5   |     |
| H                         |         |     | 10  | 1   |     | 2   |     |     | 1   | 1   |     | 1   |     |     |     |     |     |     |     |
| I                         |         |     |     | 3   |     | 2   | 2   | 1   | 1   | 4   | 1   | 1   |     | 1   | 1   |     |     |     |     |
| K                         |         | 1   | 1   | 1   |     | 1   | 3   | 1   |     |     |     |     |     |     |     | 2   |     |     |     |
| L                         |         |     | 11  | 2   | 3   | 1   | 1   | 2   | 5   |     | 1   |     | 1   |     | 1   |     |     |     |     |
| M                         |         |     |     |     | 2   | 1   | 1   |     | 1   | 1   | 1   | 1   |     |     |     |     |     | 10  |     |
| N                         |         |     |     | 1   |     | 2   |     | 1   | 1   | 2   |     |     | 1   |     |     |     |     | 2   |     |
| P                         |         |     | 5   | 1   | 4   | 3   | 1   | 2   |     |     |     | 1   | 1   | 1   | 1   |     |     |     |     |
| Q                         |         | 1   | 3   | 2   |     | 1   | 1   | 4   | 2   | 1   | 2   |     |     |     |     |     |     |     | 3   |
| R                         | 92      | 7   | 9   | 2   | 2   |     | 2   | 1   |     | 2   |     |     |     |     |     |     |     |     |     |
| S                         |         | 1   | 1   | 3   | 2   | 6   | 4   | 4   | 5   | 3   | 5   | 3   | 2   | 2   |     |     | 1   |     | 1   |
| T                         | 1       |     | 1   | 3   | 2   | 1   | 2   | 6   | 3   | 3   | 6   | 1   |     | 1   |     |     |     |     |     |
| V                         | 2       |     | 2   | 4   | 4   |     | 1   |     | 1   | 2   |     |     | 1   |     |     |     |     |     |     |
| W                         |         |     | 1   |     | 2   | 1   |     |     |     | 1   |     | 2   |     |     | 1   |     | 1   | 1   |     |
| X                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |         |     |     | 1   | 6   | 3   | 6   | 9   | 8   | 7   | 2   | 1   | 2   | 6   | 8   | 9   | 9   | 10  | 1   |
| Z                         |         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |         |     |     |     |     | 1   | 1   | 2   | 8   | 10  | 16  | 23  | 30  | 30  | 31  | 32  | 30  | 22  | 7   |
| unknown (?)               |         |     |     |     |     |     |     |     |     |     |     |     | 1   |     |     | 1   | 1   | 1   |     |
| not sequenced             | 2       | 2   | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 52  | 53  | 52  |
| sum of seq <sup>2</sup>   | 95      | 95  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 45  | 44  | 45  |
| oomcaa <sup>1</sup>       | 92      | 92  | 11  | 9   | 11  | 12  | 12  | 9   | 8   | 10  | 16  | 23  | 30  | 30  | 31  | 32  | 30  | 22  | 26  |
| mcaa <sup>1</sup>         | A       | R   | L   | G   | G   | G   | G   | Y   | Y   | -   | -   | -   | -   | -   | -   | -   | -   | F   | D   |
| rel. oomcaa <sup>3</sup>  | 97%     | 97% | 24% | 20% | 24% | 27% | 27% | 20% | 18% | 22% | 36% | 51% | 67% | 67% | 69% | 71% | 67% | 49% | 82% |
| pos occupied <sup>4</sup> | 3       | 4   | 13  | 16  | 14  | 18  | 16  | 15  | 16  | 15  | 14  | 11  | 11  | 9   | 8   | 4   | 6   | 6   | 4   |

Table 6F: Analysis of V heavy chain subgroup 5

|                           | Framework IV |      |      |     |      |     |     |     |     |      |     |     |      |  |
|---------------------------|--------------|------|------|-----|------|-----|-----|-----|-----|------|-----|-----|------|--|
| amino acid <sup>1</sup>   | 102          | 103  | 104  | 105 | 106  | 107 | 108 | 109 | 110 | 111  | 112 | 113 | sum  |  |
| A                         |              |      |      |     |      |     |     |     |     |      |     | 1   | 611  |  |
| B                         |              |      |      |     |      |     |     |     |     |      |     |     |      |  |
| C                         |              |      |      |     |      |     |     |     |     |      |     |     | 205  |  |
| D                         | 1            |      |      |     |      |     |     |     |     |      |     |     | 458  |  |
| E                         |              |      |      | 1   |      |     |     |     |     |      |     |     | 404  |  |
| F                         | 2            |      |      |     |      |     |     |     |     |      |     |     | 256  |  |
| G                         |              |      | 41   |     | 41   |     |     |     |     |      |     |     | 1065 |  |
| H                         |              |      |      |     |      |     |     |     |     |      |     |     | 44   |  |
| I                         | 9            |      |      |     |      |     |     |     | 2   |      |     |     | 588  |  |
| K                         |              |      |      | 3   |      |     |     |     |     |      |     |     | 650  |  |
| L                         | 2            |      |      |     |      |     | 25  | 1   |     |      |     |     | 549  |  |
| M                         |              |      |      |     |      |     | 8   |     |     |      |     |     | 303  |  |
| N                         |              |      |      |     |      |     |     |     |     |      |     |     | 64   |  |
| P                         | 2            |      |      |     |      | 1   |     |     |     |      | 1   |     | 414  |  |
| Q                         |              |      |      | 34  |      |     |     |     |     |      |     |     | 612  |  |
| R                         |              |      |      | 3   |      |     |     |     |     |      |     |     | 351  |  |
| S                         | 2            |      |      |     |      |     |     |     |     |      | 40  | 39  | 1545 |  |
| T                         | 1            |      |      |     |      | 40  | 8   |     | 39  |      |     |     | 604  |  |
| V                         | 11           |      |      |     |      |     |     | 40  |     | 41   |     |     | 594  |  |
| W                         |              | 43   |      |     |      |     |     |     |     |      |     |     | 432  |  |
| X                         |              |      |      |     |      |     |     |     |     |      |     |     |      |  |
| Y                         | 13           |      |      |     |      |     |     |     |     |      |     |     | 738  |  |
| Z                         |              |      |      |     |      |     |     |     |     |      |     |     |      |  |
| -                         | 2            |      |      |     |      |     |     |     |     |      |     |     | 635  |  |
| unknown (?)               |              |      |      |     |      |     |     |     |     |      |     |     | 4    |  |
| not sequenced             | 52           | 54   | 56   | 56  | 56   | 56  | 56  | 56  | 56  | 56   | 56  | 57  | 1678 |  |
| sum of seq <sup>2</sup>   | 45           | 43   | 41   | 41  | 41   | 41  | 41  | 41  | 41  | 41   | 41  | 40  |      |  |
| oomcaa <sup>3</sup>       | 13           | 43   | 41   | 34  | 41   | 40  | 25  | 40  | 39  | 41   | 40  | 39  |      |  |
| mcaa <sup>4</sup>         | Y            | W    | G    | Q   | G    | T   | L   | V   | T   | V    | S   | S   |      |  |
| rel. oomcaa <sup>5</sup>  | 29%          | 100% | 100% | 83% | 100% | 98% | 61% | 98% | 95% | 100% | 98% | 98% |      |  |
| pos occupied <sup>6</sup> | 10           | 1    | 1    | 4   | 1    | 2   | 3   | 2   | 2   | 1    | 2   | 2   |      |  |

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Table 6G: Analysis of V heavy chain subgroup 6

| Framework I               |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
|---------------------------|------|------|------|------|-----|------|------|------|------|-----|------|-----|------|-----|------|------|------|-----|-----|------|
| amino acid <sup>1</sup>   | 1    | 2    | 3    | 4    | 5   | 6    | 7    | 8    | 9    | 10  | 11   | 12  | 13   | 14  | 15   | 16   | 17   | 18  | 19  | 20   |
| A                         |      |      |      |      |     |      |      |      |      |     |      | 1   |      |     |      |      |      |     |     |      |
| B                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| C                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| D                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| E                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| F                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| G                         |      |      |      |      |     |      |      | 52   |      | 67  |      |     |      |     |      |      |      |     |     |      |
| H                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| I                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| K                         |      |      |      |      |     |      |      |      |      |     |      |     | 68   |     |      |      |      |     |     |      |
| L                         |      |      |      | 52   |     |      |      |      |      |     | 68   | 1   |      |     |      |      |      | 67  | 1   | 68   |
| M                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| N                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| P                         |      |      |      |      |     |      |      |      | 68   |     |      |     |      | 67  |      |      |      |     | 1   |      |
| Q                         | 52   |      | 52   |      | 51  | 52   |      |      |      |     |      |     |      |     |      | 68   |      |     |     |      |
| R                         |      |      |      |      | 1   |      |      |      |      | 1   |      |     |      |     |      |      |      |     |     |      |
| S                         |      |      |      |      |     |      | 52   |      |      |     |      |     |      | 1   | 68   |      |      |     | 66  |      |
| T                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| V                         |      | 52   |      |      |     |      |      |      |      |     |      | 66  |      |     |      |      |      | 68  |     |      |
| W                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     | 1   |      |
| X                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| Y                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| Z                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| -                         |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| unknown (?)               |      |      |      |      |     |      |      |      |      |     |      |     |      |     |      |      |      |     |     |      |
| not sequenced             | 22   | 22   | 22   | 22   | 22  | 22   | 22   | 22   | 6    | 6   | 6    | 6   | 6    | 6   | 6    | 6    | 6    | 6   | 6   | 6    |
| sum of seq <sup>2</sup>   | 52   | 52   | 52   | 52   | 52  | 52   | 52   | 52   | 68   | 68  | 68   | 68  | 68   | 68  | 68   | 68   | 68   | 68  | 68  | 68   |
| oomcaa <sup>3</sup>       | 52   | 52   | 52   | 52   | 51  | 52   | 52   | 52   | 68   | 67  | 68   | 66  | 68   | 67  | 68   | 68   | 68   | 67  | 66  | 68   |
| mcaa <sup>4</sup>         | Q    | V    | Q    | L    | Q   | Q    | S    | G    | P    | G   | L    | V   | K    | P   | S    | Q    | T    | L   | S   | L    |
| rel. oomcaa <sup>5</sup>  | 100% | 100% | 100% | 100% | 98% | 100% | 100% | 100% | 100% | 99% | 100% | 97% | 100% | 99% | 100% | 100% | 100% | 99% | 97% | 100% |
| pos occupied <sup>6</sup> | 1    | 1    | 1    | 1    | 2   | 1    | 1    | 1    | 1    | 2   | 1    | 3   | 1    | 2   | 1    | 1    | 1    | 2   | 3   | 1    |

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Table 6G: Analysis of V heavy chain subgroup 6

| amino acid <sup>1</sup>    |     |     |     |     |      |      |     |      |      |     | CDRI |     |     |     |     |      |     |      |     |      |  |  |
|----------------------------|-----|-----|-----|-----|------|------|-----|------|------|-----|------|-----|-----|-----|-----|------|-----|------|-----|------|--|--|
|                            | 21  | 22  | 23  | 24  | 25   | 26   | 27  | 28   | 29   | 30  | 31   | A   | B   | 32  | 33  | 34   | 35  | 36   | 37  | 38   |  |  |
| A                          | 1   |     | 67  |     |      |      |     |      |      |     |      |     |     | 66  | 67  |      |     |      |     |      |  |  |
| B                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| C                          |     | 68  |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| D                          |     |     |     |     |      |      | 68  |      |      |     | 1    |     |     |     |     |      | 1   |      |     |      |  |  |
| E                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| F                          |     |     |     |     |      |      |     |      |      | 2   |      |     |     | 1   | 1   |      |     |      |     | 1    |  |  |
| G                          |     |     | 1   |     |      | 69   |     |      |      |     |      |     | 3   | 1   | 2   |      |     |      |     |      |  |  |
| H                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      | 1   |      |     |      |  |  |
| I                          |     |     |     | 64  |      |      |     |      |      |     |      | 2   |     |     |     |      | 1   |      |     | 70   |  |  |
| K                          |     |     |     |     |      |      |     |      |      |     |      | 3   |     |     |     |      |     |      |     |      |  |  |
| L                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| M                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| N                          |     |     |     |     |      |      | 1   |      |      |     | 2    | 66  |     |     |     |      | 70  |      |     |      |  |  |
| P                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| Q                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| R                          |     |     |     |     |      |      |     |      |      |     | 2    | 1   |     |     |     |      |     |      |     | 74   |  |  |
| S                          | 1   |     |     | 1   | 69   |      |     | 69   |      | 68  | 66   |     | 67  |     | 3   |      | 1   |      |     |      |  |  |
| T                          | 67  |     |     |     |      |      |     |      |      |     | 2    | 1   | 4   |     | 1   |      |     |      |     |      |  |  |
| V                          |     |     | 1   | 4   |      |      |     |      | 70   |     |      |     |     |     | 6   |      |     |      |     | 2    |  |  |
| W                          |     | 1   |     |     |      |      |     |      |      |     |      |     |     |     |     | 74   |     | 74   |     |      |  |  |
| X                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| Y                          |     |     |     |     |      |      |     |      |      |     |      | 1   |     |     |     |      |     |      |     | 1    |  |  |
| Z                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| -                          |     |     |     |     |      |      |     |      |      |     |      |     |     |     |     |      |     |      |     |      |  |  |
| unknown (?)                |     |     |     |     |      |      |     |      |      |     | 1    |     |     |     |     |      |     |      |     |      |  |  |
| not sequenced <sup>2</sup> | 5   | 5   | 5   | 5   | 5    | 5    | 5   | 5    | 5    | 4   | 4    |     |     |     |     |      |     |      |     |      |  |  |
| sum of seq <sup>2</sup>    | 69  | 69  | 69  | 69  | 69   | 69   | 69  | 69   | 70   | 70  | 74   | 74  | 74  | 74  | 74  | 74   | 74  | 74   | 74  | 74   |  |  |
| oomcaa <sup>3</sup>        | 67  | 68  | 67  | 64  | 69   | 69   | 68  | 69   | 70   | 68  | 66   | 66  | 67  | 66  | 67  | 74   | 70  | 74   | 70  | 74   |  |  |
| mcaa <sup>4</sup>          | T   | C   | A   | I   | S    | G    | D   | S    | V    | S   | S    | N   | S   | A   | A   | W    | N   | W    | I   | R    |  |  |
| rel. oomcaa <sup>5</sup>   | 97% | 99% | 97% | 93% | 100% | 100% | 99% | 100% | 100% | 97% | 89%  | 89% | 91% | 89% | 91% | 100% | 95% | 100% | 95% | 100% |  |  |
| pos occupied <sup>6</sup>  | 3   | 2   | 3   | 3   | 1    | 1    | 2   | 1    | 1    | 2   | 5    | 6   | 3   | 4   | 5   | 1    | 5   | 1    | 4   | 1    |  |  |

Table 6G: Analysis of V heavy chain subgroup 6

|               | Framework II |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
|---------------|--------------|------|-----|-----|-----|------|------|------|------|------|------|-----|-----|-----|-----|-----|------|-----|-----|-----|--|--|--|--|
| amino acid'   | 39           | 40   | 41  | 42  | 43  | 44   | 45   | 46   | 47   | 48   | 49   | 50  | 51  | 52  | A   | B   | C    | 53  | 54  | 55  |  |  |  |  |
| A             |              |      |     | 1   |     |      |      |      |      |      |      |     | 1   |     |     |     |      | 1   |     |     |  |  |  |  |
| B             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| C             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| D             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| E             |              |      |     |     |     |      |      | 74   |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| F             |              |      |     |     |     |      |      |      |      |      |      |     |     | 2   | 1   |     |      | 1   |     |     |  |  |  |  |
| G             |              |      |     |     |     | 74   |      |      |      |      | 74   | 1   |     |     |     |     |      |     | 1   |     |  |  |  |  |
| H             |              |      |     |     |     |      |      |      |      |      |      |     |     |     | 1   |     |      |     |     |     |  |  |  |  |
| I             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| K             | 1            |      |     |     | 1   |      |      |      |      |      |      |     |     |     |     | 1   |      |     | 66  |     |  |  |  |  |
| L             | 1            |      |     |     |     | 74   |      |      | 74   |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| M             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| N             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     | 1   |     |  |  |  |  |
| P             |              |      | 73  |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| Q             | 72           |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| R             |              |      |     |     | 73  |      |      |      |      |      | 73   |     |     |     |     | 72  |      |     | 1   | 1   |  |  |  |  |
| S             |              | 74   | 1   | 73  |     |      |      |      |      |      |      |     |     |     |     | 1   |      | 72  |     |     |  |  |  |  |
| T             |              |      |     |     |     |      |      |      |      |      |      | 73  |     |     |     |     |      |     | 5   |     |  |  |  |  |
| V             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| W             |              |      |     |     |     |      |      | 74   |      |      |      |     |     |     |     |     |      |     |     | 73  |  |  |  |  |
| X             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| Y             |              |      |     |     |     |      |      |      |      |      |      |     |     | 72  | 72  |     |      |     |     |     |  |  |  |  |
| Z             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| -             |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     | 74   |     |     |     |  |  |  |  |
| unknown (?)   |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| not sequenced |              |      |     |     |     |      |      |      |      |      |      |     |     |     |     |     |      |     |     |     |  |  |  |  |
| sum of seq'   | 74           | 74   | 74  | 74  | 74  | 74   | 74   | 74   | 74   | 74   | 74   | 74  | 74  | 74  | 74  | 74  | 74   | 74  | 74  | 74  |  |  |  |  |
| oomcaa'       | 72           | 74   | 73  | 73  | 73  | 74   | 74   | 74   | 74   | 74   | 74   | 73  | 73  | 72  | 72  | 72  | 74   | 72  | 66  | 73  |  |  |  |  |
| mcaa'         | Q            | S    | P   | S   | R   | G    | L    | E    | W    | L    | G    | R   | T   | Y   | Y   | R   | -    | S   | K   | W   |  |  |  |  |
| rel. oomcaa'  | 97%          | 100% | 99% | 99% | 99% | 100% | 100% | 100% | 100% | 100% | 100% | 99% | 99% | 97% | 97% | 97% | 100% | 97% | 89% | 99% |  |  |  |  |
| pos occupied' | 3            | 1    | 2   | 2   | 2   | 1    | 1    | 1    | 1    | 1    | 1    | 2   | 2   | 2   | 3   | 3   | 1    | 3   | 5   | 2   |  |  |  |  |

Table 6G: Analysis of V heavy chain subgroup 6

|                           | CDR II |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|---------------------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| amino acid <sup>1</sup>   | 56     | 57  | 58  | 59  | 60  | 61  | 62  | 63  | 64  | 65  | 66  | 67  | 68  | 69  | 70  | 71  | 72  | 73  | 74  | 75  |  |
| A                         |        |     |     |     | 73  | 1   |     |     |     |     |     |     | 2   |     |     | 6   |     | 1   |     |     |  |
| B                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| C                         |        |     |     | 1   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| D                         |        |     | 68  |     |     | 1   |     |     |     |     |     |     |     |     | 2   |     | 73  |     |     |     |  |
| E                         | 1      |     | 3   |     |     | 7   |     |     | 1   |     |     |     |     |     |     |     |     |     |     | 2   |  |
| F                         | 7      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| G                         |        |     | 1   |     |     |     | 1   |     |     | 8   |     |     |     |     |     |     |     |     |     |     |  |
| H                         | 1      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1   |     |     |     |  |
| I                         |        |     |     |     |     | 1   |     |     |     |     |     | 65  | 2   | 71  |     |     |     | 1   |     |     |  |
| K                         |        | 1   |     |     |     |     |     |     | 67  |     |     |     |     |     |     | 1   |     |     |     | 70  |  |
| L                         | 1      |     |     |     |     | 5   |     | 2   |     |     |     |     | 4   |     |     |     |     | 1   |     |     |  |
| M                         |        |     |     |     |     |     |     |     |     |     |     |     | 1   |     |     |     |     |     |     |     |  |
| N                         | 2      | 65  | 1   |     |     |     |     |     | 1   |     |     |     |     |     | 69  |     |     |     |     |     |  |
| P                         |        |     |     |     | 1   | 1   |     |     |     |     |     |     |     |     |     |     | 66  |     |     |     |  |
| Q                         |        |     |     |     |     |     |     |     | 2   |     | 1   |     |     |     |     |     |     |     |     |     |  |
| R                         |        | 1   |     |     |     |     |     |     | 3   |     | 73  |     |     |     |     |     |     |     |     |     |  |
| S                         | 2      | 2   | 1   | 1   |     |     | 73  |     |     | 66  |     |     | 1   |     |     | 2   | 1   |     |     | 73  |  |
| T                         |        | 4   |     |     |     |     |     |     |     |     |     |     | 69  | 1   |     |     |     | 71  | 1   | 2   |  |
| V                         |        |     |     |     |     | 58  |     | 72  |     |     |     |     | 4   |     | 2   |     | 1   |     |     |     |  |
| W                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| X                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| Y                         | 60     | 1   |     | 72  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| Z                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| -                         |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| unknown (?)               |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| not sequenced             |        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| sum of seq <sup>2</sup>   | 74     | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  | 74  |  |
| oomcaa <sup>3</sup>       | 60     | 65  | 68  | 72  | 73  | 58  | 73  | 72  | 67  | 66  | 73  | 65  | 69  | 71  | 69  | 66  | 73  | 71  | 73  | 70  |  |
| mcaa <sup>4</sup>         | Y      | N   | D   | Y   | A   | V   | S   | V   | K   | S   | R   | I   | T   | I   | N   | P   | D   | T   | S   | K   |  |
| rel. oomcaa <sup>5</sup>  | 81%    | 88% | 92% | 97% | 99% | 78% | 99% | 97% | 91% | 89% | 99% | 88% | 93% | 96% | 93% | 89% | 99% | 96% | 99% | 95% |  |
| pos occupied <sup>6</sup> | 7      | 6   | 5   | 3   | 2   | 7   | 2   | 2   | 5   | 2   | 2   | 4   | 4   | 3   | 4   | 4   | 2   | 4   | 2   | 3   |  |

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Table 6G: Analysis of V heavy chain subgroup 6

| Framework III             |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
|---------------------------|------|-----|-----|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 76   | 77  | 78  | 79   | 80   | 81  | 82  | A   | B   | C   | 83  | 84  | 85  | 86  | 87   | 88   | 89  | 90  | 91  | 92  |
| A                         |      |     |     |      |      |     |     |     |     |     |     |     | 1   |     |      | 74   |     |     |     |     |
| B                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
| C                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     | 73  |
| D                         |      |     |     |      |      |     |     | 3   |     |     |     |     |     | 73  |      |      |     |     |     |     |
| E                         |      |     |     |      |      |     |     |     |     |     |     |     | 73  |     |      |      |     |     |     |     |
| F                         |      |     | 71  |      |      |     |     |     | 1   |     |     |     |     |     |      |      |     |     | 3   |     |
| G                         |      |     |     |      |      |     |     |     |     |     |     |     |     | 1   |      |      |     |     |     |     |
| H                         |      |     |     |      |      | 2   |     | 1   |     |     |     |     |     |     |      |      |     |     |     |     |
| I                         |      |     | 1   |      |      |     |     |     |     |     |     |     |     |     |      |      | 2   |     |     |     |
| K                         |      |     |     |      |      |     |     | 4   |     |     |     |     |     |     |      |      |     |     |     |     |
| L                         |      | 1   |     |      | 74   |     | 72  |     |     |     |     |     |     |     |      |      |     |     |     |     |
| M                         |      |     |     |      |      |     | 1   |     |     | 1   |     |     |     |     |      |      | 2   |     |     |     |
| N                         | 74   |     |     |      |      |     |     | 63  |     |     |     |     |     |     |      |      |     |     | 1   |     |
| P                         |      |     |     |      |      |     |     |     |     |     |     | 70  |     |     |      |      |     |     |     |     |
| Q                         |      | 72  |     |      |      | 71  |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
| R                         |      | 1   |     |      |      | 1   |     | 1   |     |     |     |     |     |     |      |      |     |     |     | 1   |
| S                         |      |     |     | 74   |      |     |     | 1   | 73  |     | 1   | 3   |     |     |      |      |     |     |     |     |
| T                         |      |     |     |      |      |     |     | 1   |     |     | 73  |     |     |     | 74   |      |     | 1   |     |     |
| V                         |      |     | 2   |      |      |     | 1   |     |     | 73  |     |     |     |     |      |      | 70  |     |     |     |
| W                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
| X                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
| Y                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     | 73  | 70  |     |
| Z                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
| -                         |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
| unknown (?)               |      |     |     |      |      |     |     |     |     |     |     |     |     |     |      |      |     |     |     |     |
| not sequenced             |      |     |     |      |      |     |     |     |     |     |     | 1   |     |     |      |      |     |     |     |     |
| sum of seq <sup>2</sup>   | 74   | 74  | 74  | 74   | 74   | 74  | 74  | 74  | 74  | 74  | 74  | 73  | 74  | 74  | 74   | 74   | 74  | 74  | 74  | 74  |
| oomcaa <sup>3</sup>       | 74   | 72  | 71  | 74   | 74   | 71  | 72  | 63  | 73  | 73  | 73  | 70  | 73  | 73  | 74   | 74   | 70  | 73  | 70  | 73  |
| mcaa <sup>4</sup>         | N    | Q   | F   | S    | L    | Q   | L   | N   | S   | V   | T   | P   | E   | D   | T    | A    | V   | Y   | Y   | C   |
| rel. oomcaa <sup>5</sup>  | 100% | 97% | 96% | 100% | 100% | 96% | 97% | 85% | 99% | 99% | 99% | 96% | 99% | 99% | 100% | 100% | 95% | 99% | 95% | 99% |
| pos occupied <sup>6</sup> | 1    | 3   | 3   | 1    | 1    | 3   | 3   | 7   | 2   | 2   | 2   | 2   | 2   | 2   | 1    | 1    | 3   | 2   | 3   | 2   |

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Table 6G: Analysis of V heavy chain subgroup 6

| CDR III                   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| amino acid <sup>1</sup>   | 93  | 94  | 95  | 96  | 97  | 98  | 99  | 100 | A   | B   | C   | D   | E   | F   | G   | H   | I   | J   | K   | 101 |
| A                         | 69  |     | 11  | 1   | 3   | 12  | 4   | 3   | 2   | 5   |     | 8   |     |     |     |     |     | 10  | 1   |     |
| B                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C                         |     |     |     |     | 1   |     | 1   |     |     | 1   |     | 1   | 1   |     |     |     |     |     |     |     |
| D                         |     |     | 19  | 4   | 3   | 7   | 4   | 3   | 1   | 6   | 1   | 1   | 1   |     |     |     |     |     |     | 62  |
| E                         |     |     | 10  | 4   | 2   | 1   | 2   | 2   | 1   | 2   |     |     |     |     |     |     | 1   |     |     |     |
| F                         | 1   |     | 1   | 1   | 1   |     | 1   | 2   | 3   |     | 2   |     |     | 1   |     |     |     |     | 38  | 4   |
| G                         | 1   |     | 16  | 4   | 15  | 15  | 11  | 8   | 6   | 2   | 5   | 1   | 8   | 6   | 1   |     |     | 17  |     |     |
| H                         |     |     |     | 1   |     | 1   |     |     | 1   | 1   | 1   | 1   |     |     |     | 1   | 1   | 1   |     |     |
| I                         |     |     |     | 1   | 2   |     | 2   |     | 5   | 1   |     |     |     |     |     |     |     |     |     |     |
| K                         |     | 1   | 1   | 1   | 1   | 1   | 1   | 1   |     |     |     | 1   |     |     |     |     |     |     |     |     |
| L                         |     |     | 1   | 8   | 4   | 2   | 3   | 2   | 1   |     |     |     |     | 1   | 5   |     |     |     | 8   |     |
| M                         |     |     |     | 1   |     |     |     | 1   |     |     | 5   |     |     |     |     |     |     |     | 11  |     |
| N                         |     |     | 1   | 3   | 1   | 2   | 1   | 1   | 1   | 3   |     | 2   |     | 1   |     | 1   | 3   |     |     |     |
| P                         |     |     |     | 10  | 4   |     | 5   | 3   |     | 5   | 1   |     | 1   |     |     |     |     |     |     |     |
| Q                         |     |     | 1   | 1   | 1   | 1   |     |     |     |     | 1   |     |     |     |     |     |     |     |     | 1   |
| R                         |     | 69  | 1   | 7   | 8   | 1   | 8   | 8   | 3   |     | 1   | 1   | 5   |     |     |     |     |     |     | 1   |
| S                         |     | 3   | 5   | 5   | 5   | 7   | 6   | 7   | 3   | 4   | 2   |     |     |     |     |     | 1   | 1   |     |     |
| T                         |     |     | 1   | 1   | 4   | 3   | 4   | 4   | 6   | 3   | 1   |     |     | 1   |     |     |     |     |     |     |
| V                         | 3   | 1   | 4   | 5   | 1   | 9   |     |     | 4   |     | 9   | 5   | 1   | 1   |     |     |     |     |     | 2   |
| W                         |     |     | 1   | 6   | 8   |     | 3   | 2   | 4   |     |     |     |     |     |     |     |     | 4   | 4   |     |
| X                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y                         |     |     |     | 6   | 4   | 2   | 2   | 2   | 6   | 6   | 2   | 4   | 2   | 1   | 8   | 8   | 12  | 12  |     |     |
| Z                         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| -                         |     |     |     | 2   | 3   | 7   | 14  | 23  | 25  | 33  | 41  | 47  | 53  | 54  | 57  | 56  | 50  | 28  | 12  | 4   |
| unknown (?)               |     |     |     |     |     |     |     |     |     |     |     |     |     | 6   | 1   | 5   |     |     |     |     |
| not sequenced             |     |     |     | 1   | 2   | 2   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   |
| sum of seq <sup>2</sup>   | 74  | 74  | 73  | 72  | 71  | 71  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  | 72  |
| oomcaa <sup>3</sup>       | 69  | 69  | 19  | 10  | 15  | 15  | 14  | 23  | 25  | 33  | 41  | 47  | 53  | 54  | 57  | 56  | 50  | 28  | 38  | 62  |
| mcaa <sup>4</sup>         | A   | R   | D   | P   | G   | G   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   | F   | D   |
| rel. oomcaa <sup>5</sup>  | 93% | 93% | 26% | 14% | 21% | 21% | 19% | 32% | 35% | 46% | 57% | 65% | 74% | 75% | 79% | 78% | 69% | 39% | 53% | 86% |
| pos occupied <sup>6</sup> | 4   | 4   | 14  | 20  | 19  | 15  | 17  | 16  | 16  | 13  | 13  | 11  | 8   | 8   | 4   | 5   | 7   | 6   | 6   | 5   |

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Table 6G: Analysis of V heavy chain subgroup 6

| Framework IV              |     |      |     |     |      |     |     |     |      |      |     |     |      |
|---------------------------|-----|------|-----|-----|------|-----|-----|-----|------|------|-----|-----|------|
| amino acid <sup>1</sup>   | 102 | 103  | 104 | 105 | 106  | 107 | 108 | 109 | 110  | 111  | 112 | 113 | sum  |
| A                         |     |      |     |     |      |     | 2   |     |      |      |     |     | 494  |
| B                         |     |      |     |     |      |     |     |     |      |      |     |     |      |
| C                         |     |      |     |     |      |     |     |     |      |      |     |     | 147  |
| D                         |     |      |     |     |      |     |     | 1   |      |      |     |     | 403  |
| E                         |     |      |     |     |      |     |     |     |      |      |     |     | 186  |
| F                         | 2   |      |     |     |      |     |     |     |      |      | 2   |     | 150  |
| G                         |     |      | 49  |     | 50   |     |     |     |      |      |     |     | 571  |
| H                         | 2   |      |     |     |      |     |     |     |      |      |     |     | 18   |
| I                         | 9   |      |     |     |      | 3   |     | 1   |      |      |     |     | 304  |
| K                         |     |      |     | 1   |      |     | 1   |     |      |      |     |     | 293  |
| L                         | 5   |      |     |     |      |     | 26  |     |      |      |     |     | 632  |
| M                         |     |      |     |     |      |     | 8   |     |      |      |     |     | 31   |
| N                         |     |      |     |     |      |     |     |     |      |      |     |     | 436  |
| P                         | 4   |      |     | 6   |      |     |     |     |      |      |     | 1   | 387  |
| Q                         |     |      |     | 40  |      |     |     |     |      |      |     |     | 539  |
| R                         |     |      |     | 2   |      |     |     |     |      |      |     |     | 495  |
| S                         | 4   |      | 1   |     |      | 1   |     |     |      |      | 43  | 46  | 1271 |
| T                         |     |      |     |     |      | 45  | 4   |     | 45   |      |     |     | 640  |
| V                         | 21  |      |     |     |      |     | 2   | 46  |      | 48   |     |     | 647  |
| W                         |     | 65   |     |     |      |     | 5   |     |      |      |     |     | 398  |
| X                         |     |      |     |     |      |     |     |     |      |      |     |     |      |
| Y                         | 19  |      |     |     |      |     |     |     |      |      |     |     | 518  |
| Z                         |     |      |     |     |      |     |     |     |      |      |     |     |      |
| -                         | 2   |      |     |     |      |     |     |     |      |      |     |     | 585  |
| unknown (?)               |     |      |     |     |      |     |     |     |      |      |     |     | 13   |
| not sequenced             | 5   | 8    | 23  | 24  | 23   | 24  | 25  | 25  | 28   | 25   | 28  | 26  | 580  |
| sum of seq <sup>2</sup>   | 68  | 65   | 50  | 49  | 50   | 49  | 48  | 48  | 45   | 48   | 45  | 47  |      |
| oomcaa <sup>3</sup>       | 21  | 65   | 49  | 40  | 50   | 45  | 26  | 46  | 45   | 48   | 43  | 46  |      |
| mcaa <sup>4</sup>         | V   | W    | G   | Q   | G    | T   | L   | V   | T    | V    | S   | S   |      |
| rel. oomcaa <sup>5</sup>  | 31% | 100% | 98% | 82% | 100% | 92% | 54% | 96% | 100% | 100% | 96% | 98% |      |
| pos occupied <sup>6</sup> | 9   | 1    | 2   | 4   | 1    | 3   | 7   | 3   | 1    | 1    | 2   | 2   |      |

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## Appendix to Tables 1A-C

A. *References of rearranged sequences**References of rearranged human kappa sequences used for alignment*

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**Claims**

1. A method of setting up one or more nucleic acid sequences encoding one or more (poly)peptide sequences suitable for the creation of libraries of (poly)peptides said (poly)peptide sequences comprising amino acid consensus sequences, said method comprising the following steps:
  - (a) deducing from a collection of at least three homologous proteins one or more (poly)peptide sequences comprising at least one amino acid consensus sequence;
  - (b) optionally, identifying amino acids in said (poly)peptide sequences to be modified so as to remove unfavorable interactions between amino acids within or between said or other (poly)peptide sequences;
  - (c) identifying at least one structural sub-element within each of said (poly)peptide sequences;
  - (d) backtranslating each of said (poly)peptide sequences into a corresponding coding nucleic acid sequence;
  - (e) setting up cleavage sites in regions adjacent to or between the ends of sub-sequences encoding said sub-elements, each of said cleavage sites:
    - (ea) being unique within each of said coding nucleic acid sequences;
    - (eb) being common to the corresponding sub-sequences of any said coding nucleic acids.
2. A method of setting up two or more sets of one or more nucleic acid sequences comprising executing the steps described in claim 1 for each of said sets with the additional provision that said cleavage sites are unique between said sets.
3. The method of claim 2 in which at least two of said sets are deduced from the same collection of at least three homologous proteins.
4. The method according to any one of claims 1 to 3, wherein said setting up further comprises the synthesis of said nucleic acid coding sequences.
5. The method according to any one of claims 1 to 4, further comprising the cloning of said nucleic acid coding sequences into a vector.

6. The method according to any one of claims 1 to 5, wherein said removal of unfavorable interactions results in enhanced expression of said (poly)peptides.
7. The method according to any one of claims 1 to 6, further comprising the steps of:
  - (f) cleaving at least two of said cleavage sites located in regions adjacent to or between the ends of said sub-sequences; and
  - (g) exchanging said sub-sequences by different sequences; and
  - (h) optionally, repeating steps (f) and (g) one or more times.
8. The method according to claim 7, wherein said different sequences are selected from the group of different sub-sequences encoding the same or different sub-elements derived from the same or different (poly)peptides.
9. The method according to claims 7 or 8, wherein said different sequences are selected from the group of:
  - (i) genomic sequences or sequences derived from genomic sequences;
  - (ii) rearranged genomic sequences or sequences derived from rearranged genomic sequences; and
  - (iii) random sequences.
10. The method according to any one of claims 1 to 9 further comprising the expression of said nucleic acid coding sequences.
11. The method according to any one of claims 1 to 10 further comprising the steps of:
  - (i) screening, after expression, the resultant (poly)peptides for a desired property;
  - (k) optionally, repeating steps (f) to (i) one or more times with nucleic acid sequences encoding one or more (poly)peptides obtained in step (i).
12. The method according to claim 11, wherein said desired property is selected from the group of optimized affinity or specificity for a target molecule, optimized enzymatic activity, optimized expression yields, optimized stability and optimized solubility.

13. The method according to any one of claims 1 to 12, wherein said cleavage sites are sites cleaved by restriction enzymes.
14. The method according to any one of claims 1 to 13, wherein said structural sub-elements comprise between 1 and 150 amino acids.
15. The method according to claim 14, wherein said structural sub-elements comprise between 3 and 25 amino acids.
16. The method according to any one of claims 1 to 15, wherein said nucleic acid is DNA.
17. The method according to any one of claims 1 to 16, wherein said (poly)peptides have an amino acid pattern characteristic of a particular species.
18. The method according to claim 17, wherein said species is human.
19. The method according to any one of claims 1 to 18, wherein said (poly)peptides are at least part of members or derivatives of the immunoglobulin superfamily.
20. The method according to claim 19, wherein said members or derivatives of the immunoglobulin superfamily are members or derivatives of the immunoglobulin family.
21. The method according to claim 19 or 20, wherein said (poly)peptides are or are derived from heavy or light chain variable regions wherein said structural sub-elements are framework regions (FR) 1, 2, 3, or 4 or complementary determining regions (CDR) 1, 2, or 3.
22. The method according to claim 20 or 21, wherein said (poly)peptides are or are derived from the HuCAL consensus genes:  
V $\kappa$ 1, V $\kappa$ 2, V $\kappa$ 3, V $\kappa$ 4, V $\lambda$ 1, V $\lambda$ 2, V $\lambda$ 3, VH1A, VH1B, VH2, VH3, VH4, VH5, VH6, C $\kappa$ , C $\lambda$ , CH1 or any combination of said HuCAL consensus genes.
23. The method according to any one of claims 20 to 22, wherein said derivative of said immunoglobulin family or said combination is an Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragment.

24. The method according to claims 22 to 23, wherein said derivative is an scFv fragment comprising the combination of HuCAL VH3 and HuCAL V $\lambda$ 2 consensus genes that comprises a random sub-sequence encoding the heavy chain CDR3 sub-element.
25. The method according to any one of claims 1 to 24, wherein at least part of said (poly)peptide sequences or (poly)peptides is connected to a sequence encoding at least one additional moiety or to at least one additional moiety, respectively.
26. The method according to claim 25, wherein said connection is formed via a contiguous nucleic acid sequence or amino acid sequence, respectively.
27. The method according to claims 25 to 26, wherein said additional moiety is a toxin, a cytokine, a reporter enzyme, a moiety being capable of binding a metal ion, a peptide, a tag suitable for detection and/or purification, or a homo- or hetero-association domain.
28. The method according to any one of claims 10 to 27, wherein the expression of said nucleic acid sequences results in the generation of a repertoire of biological activities and/or specificities, preferably in the generation of a repertoire based on a universal framework.
29. A nucleic acid sequence obtainable by the method according to any of claims 1 to 28.
30. A collection of nucleic acid sequences obtainable by the method according to any of claims 1 to 28.
31. A recombinant vector obtainable by the method according to any of claims 5 to 28.
32. A collection of recombinant vectors obtainable by the method according to any of claims 5 to 30.
33. A host cell transformed with the recombinant vector according to claim 31.



34. A collection of host cells transformed with the collection of recombinant vectors according to claim 32.
35. A method of producing a (poly)peptide or a collection of (poly)peptides as defined in any of claims 1 to 28 comprising culturing the host cell according to claim 33 or the collection of host cells according to claim 34 under suitable conditions and isolating said (poly)peptide or said collection of (poly)peptides.
36. A (poly)peptide devisable by the method according to any one of claims 1 to 3, encoded by the nucleic acid sequence according to claim 29 or obtainable by the method according to any one of claims 4 to 28 or 35.
37. A collection of (poly)peptides devisable by the method according to any one of claims 1 to 3, encoded by the collection of nucleic acid sequences according to claim 30 or obtainable by the method according to any one of claims 4 to 28 or 35.
38. A vector suitable for use in the method according to any of claims 5 to 28 and 35 characterized in that said vector is essentially devoid of any cleavage site as defined in claim 1(e) and 2.
39. The vector according to claim 38 which is an expression vector.
40. A kit comprising at least one of;
- (a) a nucleic acid sequence according to claim 29;
  - (b) a collection of nucleic acid sequences according to claim 30;
  - (c) a recombinant vector according to claim 31;
  - (d) a collection of recombinant vectors according to claim 32;
  - (e) a (poly)peptide according to claim 36;
  - (f) a collection of (poly)peptides according to claim 37;
  - (g) a vector according to claim 38 or 39; and optionally,
  - (h) a suitable host cell for carrying out the method according to claim 35.
41. A method of designing two or more genes encoding a collection of two or more proteins, comprising the steps of:

- (a) either
  - (aa) identifying two or more homologous gene sequences, or
  - (ab) analyzing at least three homologous genes, and deducing two or more consensus gene sequences therefrom,
- (b) optionally, modifying codons in said consensus gene sequences to remove unfavourable interactions between amino acids in the resulting proteins,
- (c) identifying sub-sequences which encode structural sub-elements in said consensus gene sequences
- (d) modifying one or more bases in regions adjacent to or between the ends of said sub-sequences to define one or more cleavage sites, each of which:
  - (da) are unique within each consensus gene sequence,
  - (db) do not form compatible sites with respect to any single sub-sequence,
  - (dc) are common to all homologous sub-sequences.

42. A method of preparing two or more genes encoding a collection of two or more proteins, comprising the steps of :

- (a) designing said genes according to claim 41, and
- (b) synthesizing said genes.

43. A collection of genes prepared according to the method of claim 42.

44. A collection of two or more genes derived from gene sequences which:

- (a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and

- (b) carry cleavage sites, each of which:
  - (ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,
  - (bb) are unique within each gene sequence,
  - (bc) do not form compatible sites with respect to any single sub-sequence, and
  - (bd) are common to all homologous sub-sequences.
- 45. The collection of genes according to either of claims 43 or 44 in which each of said gene sequences has a nucleotide composition characteristic of a particular species.
- 46. The collection of genes according to claim 45 in which said species is human.
- 47. The collection of genes according to any of claims 43 to 46 in which one or more of said gene sequences encodes at least part of a member of the immunoglobulin superfamily, preferably of the immunoglobulin family.
- 48. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody heavy chains.
- 49. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody light chains.
- 50. A collection of vectors comprising a collection of gene sequences according to any of claims 43 to 49.

51. The collection of vectors according to claim 50 comprising the additional feature that the vector does not comprise any cleavage site that is contained in the collection of genes according to any of claims 43 to 49.
52. A method for identifying one or more genes encoding one or more proteins having a desirable property, comprising the steps of:
- (a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins.
  - (b) screening said collection to isolate one or more proteins having a desired property,
  - (c) identifying the genes encoding the proteins isolated in step (b),
  - (d) optionally, excising from the genes encoding the proteins isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or more second sub-sequences encoding structural sub-elements, to generate new vectors according to either of claims 50 or 51,
  - (e) optionally, repeating steps (a) to (c).
53. A method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of:
- (a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins,
  - (b) screening said collection to isolate one or more antibody fragments which bind to said target,
  - (c) identifying the genes encoding the proteins isolated in step (b),
  - (d) optionally, excising from the genes encoding the antibody fragments isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or

more second sub-sequences encoding structural sub-generate new vectors according to either of claims 50 or 51,

- (e) optionally, repeating steps (a) to (c).

54. A kit comprising two or more genes derived from gene sequences which:

- (a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and
- (b) carry cleavage sites, each of which:
  - (ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,
  - (bb) are unique within each gene sequence,
  - (bc) do not form compatible sites with respect to any single sub-sequence, and
  - (bd) are common to all homologous sub-sequences.

55. A kit comprising two or more genetic sub-sequences which encode structural sub-elements, which can be assembled to form genes, and which carry cleavage sites, each of which:

- (a) lie at or adjacent to the ends of said genetic sub-sequences,
- (b) do not form compatible sites with respect to any single sub-sequence, and
- (d) are common to all homologous sub-sequences.

Figure 1: construction of a synthetic human antibody library based on consensus sequences

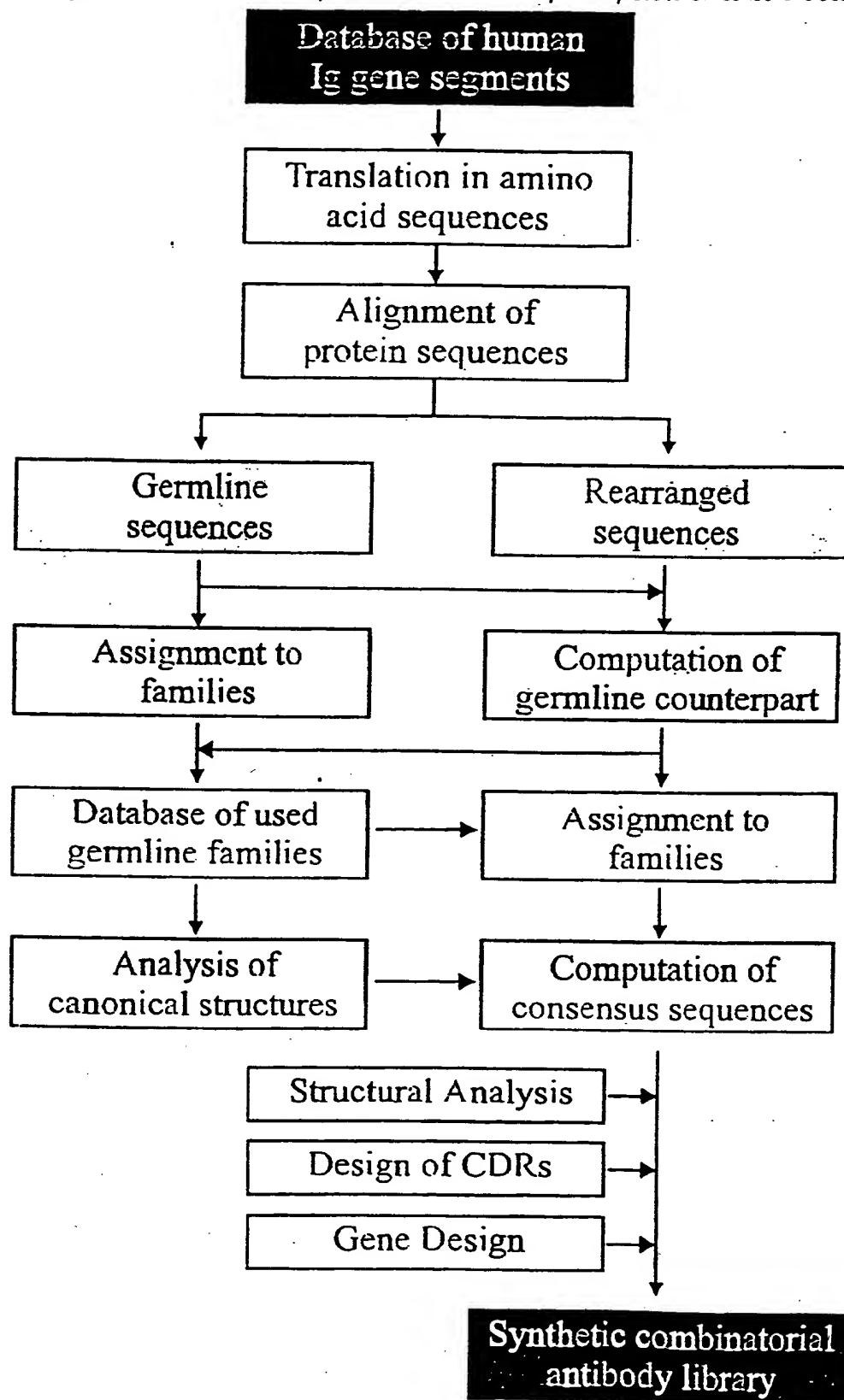


Figure 2A: VL kappa consensus sequences

| framework 1 |   |   |   |   |   |   |   |   |    |    |    |    |    | CDRI |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|-------------|---|---|---|---|---|---|---|---|----|----|----|----|----|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1           | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15   | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
| Vk1         | D | I | Q | M | T | Q | S | P | S  | S  | L  | S  | A  | S    | V  | G  | D  | R  | V  | T  | I  | T  | C  | R  | A  | S  | Q  | -  | -  |
| Vk2         | D | I | V | M | T | Q | S | P | L  | S  | L  | P  | V  | T    | P  | G  | E  | P  | A  | S  | I  | S  | C  | R  | S  | S  | Q  | S  | L  |
| Vk3         | D | I | V | L | T | Q | S | P | A  | T  | L  | S  | L  | S    | P  | G  | E  | R  | A  | T  | L  | S  | C  | R  | A  | S  | Q  | S  | -  |
| Vk4         | D | I | V | M | T | Q | S | P | D  | S  | L  | A  | V  | S    | L  | G  | E  | R  | A  | T  | I  | N  | C  | R  | S  | S  | Q  | S  | V  |

| CDRI |   |   |    |    |    |    |    |    |    |    |    |    |    | framework 2 |    |    |    |    |    |    |    |    |    |    |    |    |    | CDRI II |    |   |  |  |  |  |  |  |  |  |  |  |  |
|------|---|---|----|----|----|----|----|----|----|----|----|----|----|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|---------|----|---|--|--|--|--|--|--|--|--|--|--|--|
| D    | F | F | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39          | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53      | 54 |   |  |  |  |  |  |  |  |  |  |  |  |
| Vk1  | - | - | -  | G  | I  | S  | S  | Y  | L  | A  | W  | Y  | Q  | Q           | K  | P  | G  | K  | A  | P  | K  | L  | L  | I  | Y  | A  | A  | S       | S  | L |  |  |  |  |  |  |  |  |  |  |  |
| Vk2  | H | S | -  | N  | G  | Y  | N  | Y  | L  | D  | W  | Y  | L  | Q           | K  | P  | G  | Q  | S  | P  | Q  | L  | L  | I  | Y  | L  | G  | S       | N  | R |  |  |  |  |  |  |  |  |  |  |  |
| Vk3  | - | - | -  | V  | S  | S  | S  | Y  | L  | A  | W  | Y  | Q  | Q           | K  | P  | G  | Q  | A  | P  | R  | L  | L  | I  | Y  | G  | A  | S       | S  | R |  |  |  |  |  |  |  |  |  |  |  |
| Vk4  | Y | S | S  | N  | N  | K  | N  | Y  | L  | A  | W  | Y  | Q  | Q           | K  | P  | G  | Q  | P  | P  | K  | L  | L  | I  | Y  | W  | A  | S       | T  | R |  |  |  |  |  |  |  |  |  |  |  |

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| framework 3  |   |   | CDRIII |   |   | framework 4 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|--------------|---|---|--------|---|---|-------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| V $\kappa$ 1 | T | Y | Y      | C | Q | Q           | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V | E | I | K | R | T |
| V $\kappa$ 2 | V | Y | Y      | C | Q | Q           | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V | E | I | K | R | T |
| V $\kappa$ 3 | V | Y | Y      | C | Q | Q           | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V | E | I | K | R | T |
| V $\kappa$ 4 | V | Y | Y      | C | Q | Q           | H | Y | T | T | P | P | T | F | G | Q | G | T | K | V | E | I | K | R | T |



Figure 2B: VL lambda consensus sequences

| framework 1 |   |   |   |   |   |   |   |   |   |    |    |    |    | CDRI |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |
|-------------|---|---|---|---|---|---|---|---|---|----|----|----|----|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|
|             | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14   | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |   |   |
| VA1         | Q | S | V | L | T | Q | P | P | S | -  | V  | S  | G  | A    | P  | G  | Q  | R  | V  | T  | I  | S  | C  | S  | G  | S  | S  | S  | I |   |
| VA2         | Q | S | A | L | T | Q | P | A | S | -  | V  | S  | G  | S    | P  | G  | Q  | S  | I  | T  | I  | S  | C  | T  | G  | T  | S  | S  | D | V |
| VA3         | S | Y | E | L | T | Q | P | P | S | -  | V  | S  | V  | A    | P  | G  | Q  | T  | A  | R  | I  | S  | C  | S  | G  | D  | A  | -  | - | L |

| CDRI |    |    |    |    | framework 2 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | CDR II |    |    |    |    |    |    |   |   |
|------|----|----|----|----|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--------|----|----|----|----|----|----|---|---|
| 29   | 30 | 31 | 32 | 33 | 34          | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51     | 52 | 53 | 54 | 55 | 56 | 57 |   |   |
| VA1  | G  | S  | N  | -  | Y           | V  | S  | W  | Y  | Q  | Q  | L  | P  | G  | T  | A  | P  | K  | L  | L  | I  | Y      | D  | N  | N  | Q  | R  | P  | S | G |
| VA2  | G  | G  | Y  | N  | Y           | V  | S  | W  | Y  | Q  | Q  | H  | P  | G  | K  | A  | P  | K  | L  | M  | I  | Y      | D  | V  | S  | N  | R  | P  | S | G |
| VA3  | G  | D  | K  | -  | Y           | A  | S  | W  | Y  | Q  | Q  | K  | P  | G  | Q  | A  | P  | V  | L  | V  | I  | Y      | D  | D  | S  | D  | R  | P  | S | G |

Figure 2B: VL lambda consensus sequences

| framework 3 |   |   |   |   |   |   |   |   |   |
|-------------|---|---|---|---|---|---|---|---|---|
| 58          | V | P | D | R | F | S | G | S | K |
| 59          | V | S | N | R | F | S | G | S | K |
| 60          | I | P | E | R | F | S | G | S | N |
| 61          |   |   |   |   |   |   |   |   |   |
| 62          |   |   |   |   |   |   |   |   |   |
| 63          |   |   |   |   |   |   |   |   |   |
| 64          |   |   |   |   |   |   |   |   |   |
| 65          |   |   |   |   |   |   |   |   |   |
| 66          |   |   |   |   |   |   |   |   |   |
| 67          |   |   |   |   |   |   |   |   |   |
| 68          |   |   |   |   |   |   |   |   |   |
| 69          |   |   |   |   |   |   |   |   |   |
| 70          |   |   |   |   |   |   |   |   |   |
| 71          |   |   |   |   |   |   |   |   |   |
| 72          |   |   |   |   |   |   |   |   |   |
| 73          |   |   |   |   |   |   |   |   |   |
| 74          |   |   |   |   |   |   |   |   |   |
| 75          |   |   |   |   |   |   |   |   |   |
| 76          |   |   |   |   |   |   |   |   |   |
| 77          |   |   |   |   |   |   |   |   |   |
| 78          |   |   |   |   |   |   |   |   |   |
| 79          |   |   |   |   |   |   |   |   |   |
| 80          |   |   |   |   |   |   |   |   |   |
| 81          |   |   |   |   |   |   |   |   |   |
| 82          |   |   |   |   |   |   |   |   |   |
| 83          |   |   |   |   |   |   |   |   |   |
| 84          |   |   |   |   |   |   |   |   |   |
| 85          |   |   |   |   |   |   |   |   |   |
| 86          |   |   |   |   |   |   |   |   |   |
| 87          |   |   |   |   |   |   |   |   |   |

| framework 4 |   |   |   |   |   |   |   |   |   |
|-------------|---|---|---|---|---|---|---|---|---|
| 88          | C | Q | Q | H | Y | T | T | P | P |
| 89          | C | Q | Q | H | Y | T | T | P | P |
| 90          | C | Q | Q | H | Y | T | T | P | P |
| 91          |   |   |   |   |   |   |   |   |   |
| 92          |   |   |   |   |   |   |   |   |   |
| 93          |   |   |   |   |   |   |   |   |   |
| 94          |   |   |   |   |   |   |   |   |   |
| 95          |   |   |   |   |   |   |   |   |   |
| 96          |   |   |   |   |   |   |   |   |   |
| 97          |   |   |   |   |   |   |   |   |   |
| 98          |   |   |   |   |   |   |   |   |   |
| 99          |   |   |   |   |   |   |   |   |   |
| 100         |   |   |   |   |   |   |   |   |   |
| 101         |   |   |   |   |   |   |   |   |   |
| 102         |   |   |   |   |   |   |   |   |   |
| 103         |   |   |   |   |   |   |   |   |   |
| 104         |   |   |   |   |   |   |   |   |   |
| 105         |   |   |   |   |   |   |   |   |   |
| 106         |   |   |   |   |   |   |   |   |   |
| 107         |   |   |   |   |   |   |   |   |   |

Figure 2C: V heavy chain consensus sequences

| framework 1 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
|-------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|
|             | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |   |
| VH1A        | Q | V | Q | L | V | Q | S | G | A | E  | V  | K  | K  | P  | G  | S  | S  | V  | K  | V  | S  | C  | K  | A  | S  | G  | G  | T  | F  | S  |   |
| VH1B        | Q | V | Q | L | V | Q | S | G | A | E  | V  | K  | K  | P  | G  | A  | S  | V  | K  | V  | S  | C  | K  | A  | S  | G  | G  | Y  | T  | F  | T |
| VH2         | Q | V | Q | L | K | E | S | G | P | A  | L  | V  | K  | P  | T  | Q  | T  | L  | T  | L  | S  | C  | T  | F  | S  | G  | F  | S  | L  | S  |   |
| VH3         | E | V | Q | L | V | E | S | G | G | L  | V  | Q  | P  | G  | S  | L  | R  | L  | S  | L  | S  | C  | A  | A  | S  | G  | F  | T  | F  | S  |   |
| VH4         | Q | V | Q | L | Q | E | S | G | P | G  | L  | V  | K  | P  | S  | E  | T  | L  | S  | L  | S  | C  | T  | V  | S  | G  | G  | S  | I  | S  |   |
| VH5         | E | V | Q | L | V | Q | S | G | A | E  | V  | K  | K  | P  | G  | E  | S  | L  | K  | I  | S  | C  | K  | G  | S  | G  | Y  | S  | F  | T  |   |
| VH6         | Q | V | Q | L | Q | Q | S | G | P | G  | L  | V  | K  | P  | S  | Q  | T  | L  | S  | L  | S  | C  | A  | I  | S  | G  | D  | S  | V  | S  |   |

| CDRI |   |   |    |    |    |    |    |    |    | framework 2 |    |    |    |    |    |    |    |    |    | CDR II |    |    |    |   |   |   |    |    |    |    |    |   |   |
|------|---|---|----|----|----|----|----|----|----|-------------|----|----|----|----|----|----|----|----|----|--------|----|----|----|---|---|---|----|----|----|----|----|---|---|
| 31   | A | 8 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39          | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49     | 50 | 51 | 52 | A | B | C | 53 | 54 | 55 | 56 | 57 |   |   |
| VH1A | S | - | -  | Y  | A  | I  | S  | W  | V  | R           | Q  | A  | P  | G  | Q  | G  | L  | E  | W  | M      | G  | G  | I  | I | P | - | -  | -  | I  | F  | G  | T | A |
| VH1B | S | - | -  | Y  | Y  | M  | H  | W  | V  | R           | Q  | A  | P  | G  | Q  | G  | L  | E  | W  | M      | G  | W  | I  | N | P | - | -  | -  | N  | S  | G  | G | T |
| VH2  | T | S | G  | V  | G  | V  | G  | W  | I  | R           | Q  | P  | P  | G  | K  | A  | L  | E  | W  | L      | A  | L  | I  | D | - | - | -  | -  | W  | D  | D  | D | K |
| VH3  | S | - | -  | Y  | A  | M  | S  | W  | V  | R           | Q  | A  | P  | G  | K  | G  | L  | E  | W  | V      | S  | A  | I  | S | G | - | -  | -  | S  | G  | G  | S | T |
| VH4  | S | - | -  | Y  | Y  | W  | S  | W  | I  | R           | Q  | P  | P  | G  | K  | G  | L  | E  | W  | I      | G  | Y  | I  | Y | - | - | -  | -  | Y  | S  | G  | S | T |
| VH5  | S | - | -  | Y  | W  | I  | G  | W  | V  | R           | Q  | M  | P  | G  | K  | G  | L  | E  | W  | M      | G  | I  | I  | Y | P | - | -  | -  | G  | D  | S  | D | T |
| VH6  | S | N | S  | A  | A  | W  | N  | W  | I  | R           | Q  | S  | P  | G  | R  | G  | L  | E  | W  | L      | G  | R  | T  | Y | Y | R | -  | -  | S  | K  | W  | Y | N |

Figure 2C: V heavy chain consensus sequences

| CDRII |    |    |    |    |    |    |    |    |    | framework 3 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |
|-------|----|----|----|----|----|----|----|----|----|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|
| VH1A  | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67          | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 |   |   |   |
| VH1B  | N  | Y  | A  | Q  | K  | F  | Q  | G  | R  | V           | T  | I  | T  | A  | D  | E  | S  | T  | S  | T  | A  | Y  | M  | E  | L  | S  | S  | L  | R | S | E |
| VH2   | N  | Y  | A  | Q  | K  | F  | Q  | G  | R  | V           | T  | M  | T  | R  | D  | T  | S  | I  | S  | T  | A  | Y  | M  | E  | L  | S  | S  | L  | R | S | E |
| VH3   | Y  | Y  | S  | T  | S  | L  | K  | T  | R  | L           | T  | I  | S  | K  | D  | T  | S  | K  | N  | Q  | V  | V  | L  | T  | M  | T  | N  | M  | D | P | V |
| VH4   | Y  | Y  | A  | D  | S  | V  | K  | G  | R  | F           | T  | I  | S  | R  | D  | N  | S  | K  | N  | T  | L  | Y  | L  | Q  | M  | N  | S  | L  | R | A | E |
| VH5   | N  | Y  | N  | P  | S  | L  | K  | S  | R  | V           | T  | I  | S  | V  | D  | T  | S  | K  | N  | Q  | F  | S  | L  | K  | L  | S  | S  | V  | T | A | A |
| VH6   | R  | Y  | S  | P  | S  | F  | Q  | G  | Q  | V           | T  | I  | S  | A  | D  | K  | S  | I  | S  | T  | A  | Y  | L  | Q  | W  | S  | S  | L  | K | A | S |
|       | D  | Y  | A  | V  | S  | V  | K  | S  | R  | I           | T  | I  | N  | P  | D  | T  | S  | K  | N  | Q  | F  | S  | L  | Q  | L  | N  | S  | V  | T | P | E |

| framework 3 |    |    |    |    |    |    |    |    |    | CDRIII |    |    |    |    |     |   |   |   |     | framework 4 |     |     |     |     |     |     |     |     |     |     |     |   |
|-------------|----|----|----|----|----|----|----|----|----|--------|----|----|----|----|-----|---|---|---|-----|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|
| VH1A        | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95     | 96 | 97 | 98 | 99 | 100 | A | B | C | 101 | 102         | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 |   |
| VH1B        | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G  | F   | Y | A | M | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S   | S |
| VH2         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G  | F   | Y | A | M | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S   | S |
| VH3         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G  | F   | Y | A | M | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S   | S |
| VH4         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G  | F   | Y | A | M | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S   | S |
| VH5         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G  | F   | Y | A | M | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S   | S |
| VH6         | D  | T  | A  | V  | Y  | Y  | C  | A  | R  | W      | G  | G  | D  | G  | F   | Y | A | M | D   | Y           | W   | G   | Q   | Q   | G   | T   | L   | V   | T   | V   | S   | S |

Figure 3A: V kappa 1 (Vk1) gene sequence

```

.D I Q M T Q S P S S L S A S V G D
ECORV
~~~~~
BanII
~~~~~
GATATCCAGA TGACCCAGAG CCCGTCTAGC CTGAGCGCGA GCGTGGGTGA
CTATAGGTCT ACTGGGTCTC GGCAGATCG GACTCGCGCT CGCACCCACT

R V T I T C R A S Q G I S S Y L
PstI
~~~~~
TCGTGTGACC ATTACCTGCA GAGGAGCCA GGCATTAGC AGCTATCTGG
AGCACACTGG TAATGGACGT CTCGCTCGGT CCCGTAATCG TCGATAGACC

A W Y Q Q K P G K A P K L L I Y A
KpnI SexAI AseI
~~~~~
CGTGGTACCA GCAGAAACCA GGTAAAGCAC CGAAACTATT AATTATGCA
GCACCATGGT CGTCTTTGGT CCATTTCGTG GCTTTGATAA TTAATACGT

A S S L Q S G V P S R F S G S G S
SandI BamHI
~~~~~
GCCAGCAGCT TGCAAAGCGG GGTCCCGTCC CGTTTAGCG GCTCTGGATC

```

Figure 3A: V kappa 1 (Vk1) gene sequence (continued)

CGGTCGTCGA ACGTTTCGCC CCAGGGCAGG GCAAAATCGC CGAGACCTAG

G T D F T L T I S S L Q P E D F

Eco57I

~~~~~

BamHI

BbsI

~~~~~

CGGCACTGAT TTACCCTGA CCATTAGCAG CCGCAACCT GAAGACTTG  
GCCGTGACTA AAATGGGACT GGTAATCGTC GGACGTTGGA CTTCTGAAAC

A T Y Y C Q Q H Y T T P P T F G Q

MSCI

~~~~~

CGACCTATTA TTGCCAGCAG CATTATACCA CCGGCCGAC CTTGGCCAG  
GCTGGATAAT AACGGTCGTC GTAATATGGT GGGCGGGCTG GAAACCGGTC

G T K V E I K R T

BsiWI

~~~~~

GGTACGAAAG TTGAAATTAA ACGTACG  
CCATGCTTC AACTTTAATT TGCATGC

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Figure 3B: V kappa 2 (Vk2) gene sequence

```

D I V M T Q S P L S L P V T P G E
EcoRV      BanII
~~~~~
GATATCGTGA TGACCCAGAG CCCACTGAGC CTGCCAGTGA CTCCGGGCGGA
CTATAGCACT ACTGGGTCTC GGTGACTCG GACGGTCACT GAGGCCCGCT

P A S I S C R S S Q S L L H S N
PstI
~~~~~
GCCTGCGAGC ATTAGCTGCA GAAGCAGCCA AAGCCTGCTG CATAGCAACG
CGGACGCTCG TAATCGACGT CTTCGTCGGT TTCGGACGAC GTATCGTTGC

G Y N Y L D W Y L Q K P G Q S P Q
KpnI      SexAI
~~~~~
GCTATAACTA TCTGGATTGG TACCTTCAA AACCAGGTCA AAGCCCGCAG
CGATATTGAT AGACCTAACC ATGGAAGTTT TTGGTCCAGT TTCGGGCGTC

L L I Y L G S N R A S G V P D R F
AseI      SmaI
~~~~~
CTATTAAATTT ATCTGGGCAG CAACCGTGCC AGTGGGTCC CGGATCGTTT
GATAATTAAA TAGACCCGTC GTTGGCACGG TCACCCCGAG GCCTAGCAAA

```

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Figure 3B: V kappa 2 (Vk2) gene sequence (continued)

|            |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
|------------|------------|------------|------------|------------|---|---|---|---|---|---|---|---|---|---|---|---|
| S          | G          | S          | G          | S          | G | T | D | F | T | L | K | I | S | R | V |   |
| BamHI      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| TAGCGGCTCT | GGATCCGGCA | CCGATTTTAC | CCTGAAAATT | AGCCGTGTGG |   |   |   |   |   |   |   |   |   |   |   |   |
| ATCGCCGAGA | CCTAGGCCGT | GGCTAAAATG | GGACTTTTAA | TCGGCACACC |   |   |   |   |   |   |   |   |   |   |   |   |
| E          | A          | E          | D          | V          | G | V | Y | Y | C | Q | Q | H | Y | T | T | P |
| Eco57I     |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| BbsI       |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| AAGCTGAAGA | CGTGGCGTG  | TATTATGCC  | AGCAGCATTA | TACCACCCCG |   |   |   |   |   |   |   |   |   |   |   |   |
| TTCGACTTCT | GCACCCGCAC | ATAATAACGG | TCGTCGTAAT | ATGGTGGGGC |   |   |   |   |   |   |   |   |   |   |   |   |
| P          | T          | F          | G          | Q          | G | T | K | V | E | I | K | R | T |   |   |   |
| MscI       |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| CCGACCTTTG | GCCAGGGTAC | GAAAGTTGAA | ATTAAACGTA | CG         |   |   |   |   |   |   |   |   |   |   |   |   |
| GGCTGGAAC  | CGGTCCCATG | CTTCAACTT  | TAATTGCAT  | GC         |   |   |   |   |   |   |   |   |   |   |   |   |
| BsiWI      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |

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Figure 3C: V kappa 3 (Vk3) gene sequence

```

D I V L T Q S P A T L S L S P G E
EcoRV                               BanII
~~~~~                               ~~~~~
GATATCGTGC TGACCCAGAG CCCGGCGACC CTGAGCCTGT CTCGGGGCGGA
CTATAGCAGC ACTGGGTCTC GGGCCGCTGG GACTCGGACA GAGGCCCGCT

R A T L S C R A S Q S V S S S Y
                               PstI
                               ~~~~~
ACGTGCGACC CTGAGCTGCA GAGCGAGCCA GAGCGTGAGC AGCAGCTATC
TGCACGCTGG GACTCGACGT CTCGCTCGGT CTCGCACTCG TCGTCGATAG

L A W Y Q Q K P G Q A P R L L I Y
      KpnI      SexAI      AseI
      ~~~~~      ~~~~~      ~~~~~
TGGCGTGGTA CCAGCAGAAA CCAGGTCAAG CACCGCGTCT ATTAATTAT
ACCGCACCAT GTCGTCTTT GGTCCAGTTC GTGGCGCAGA TAATTAAATA

G A S S R A T G V P A R F S G S G
      SandI      ~~~~~      BamHI
      ~~~~~      ~~~~~
GGCGCGAGCA GCCGTGCAAC TGGGGTCCCCG GCGCGTTTAA GCGGCTCTGG

```

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Figure 3C: V kappa 3 (Vk3) gene sequence (continued)

CCGCGGCTCGT CGGCACGTTG ACCCCAGGGC CGCGCAAAT CGCCGAGACC

S G T D F T L T I S S L E P E D  
Eco57I  
~~~~~

BamHI  
~~~~~  
ATCCGGCAGG GATTTACCC TGACCATTAG CAGCCTGGAA CCTGAAGACT  
TAGGCCGTGC CTAAATGGG ACTGGTAATC GTCGGACCTT GGAATTCTGA

F A V Y Y C Q Q H Y T T P P T F G  
MscI  
~~~~~

TTGCGGTGTA TTATTGCCAG CAGCATTATA CCACCCCGCC GACCTTTGGC  
AACGCCACAT AATAACGGTC GTCGTAATAT GTGGGGCGG CTGGAAACCG

Q G T K V E I K R T  
MscI  
~~~~~  
CAGGTACGA AAGTTGAAAT TAAACGTACG  
GTCCCATGCT TTCAACTTAA ATTGCATGC

Figure 3D: V kappa 4 (Vk4) gene sequence

```

D I V M T Q S P D S L A V S L G E
EcoRV          BanII
~~~~~
GATATCGTGA TGACCCAGAG CCGGATAGC CTGGCGGTGA GCCTGGGCGA
CTATAGCACT ACTGGGTCTC GGGCCTATCG GACCGCCACT CGGACCCGCT

R A T I N C R S S Q S V L Y S S
PstI
~~~~~
ACGTGCGACC ATTAAGTGCA GAAGCAGCCA GAGCGTGCTG TATAGCAGCA
TGCACGCTGG TAATTGACGT CTTCGTCGGT CTCGCACGAC ATATCGTCGT

N N K N Y L A W Y Q Q K P G Q P P
KpnI          SexAI
~~~~~
ACAACAAAAA CTATCTGGCG TGGTACCAGC AGAAACCAGG TCAGCCGCCG
TGTTGTTTTT GATAGACCGC ACCATGGTCC TCTTTGGTCC AGTCGGCGGC

K L L I Y W A S T R E S G V P D R
AseI          SmaI
~~~~~
AAACTATTAA TTTATTGGC ATCCACCCGT GAAAGCGGGG TCCCGGATCG
TTTGATAATT AAATAACCCG TAGGTGGGCA CTTTCGCCCC AGGGCCTAGC

```

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Figure 3D: V kappa 4 (Vκ4) gene sequence (continued)

|            |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
|------------|------------|------------|-------------|------------|---|---|---|---|---|---|---|---|---|---|---|
| F          | S          | G          | S           | G          | S | G | T | D | F | T | L | T | I | S | S |
| BamHI      |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| TTTTAGCGGC | TCTGGATCCG | GCACTGATTT | TACCCCTGACC | ATTTCGTCCC |   |   |   |   |   |   |   |   |   |   |   |
| AAAATCGCCG | AGACCTAGGC | CGTGAATAAA | ATGGGACTGG  | TAAAGCAGGG |   |   |   |   |   |   |   |   |   |   |   |
| L          | Q          | A          | E           | D          | V | A | V | Y | C | Q | Q | H | Y | T | T |
| Eco57I     |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| BbsI       |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| TGCAAGCTGA | AGACGTGGCG | GTGTATTATT | GCCAGCAGCA  | TTATACCACC |   |   |   |   |   |   |   |   |   |   |   |
| ACGTTGCACT | TCTGCACCCG | CACATAATAA | CGGTCGTCGT  | AATATGGTGG |   |   |   |   |   |   |   |   |   |   |   |
| P          | P          | T          | F           | G          | Q | G | T | K | V | E | I | K | R | T |   |
| MscI       |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| CCGCCGACCT | TTGGCCAGGG | TACGAAAGTT | GAAATTAAAC  | GTACG      |   |   |   |   |   |   |   |   |   |   |   |
| GGCGGCTGGA | AACCGGTCCC | ATGCTTTCAA | CTTTAATTG   | CATGC      |   |   |   |   |   |   |   |   |   |   |   |
| BsiWI      |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~      |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |

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Figure 4A: V lambda 1 (Vλ1) gene sequence

Q S V L T Q P S V S G A P G Q R  
e 4A: V lambda 1 (Vλ1) gene sequence  
SexAI

CAGAGCGTGC TGACCCAGCC GCCTTCAGTG AGTGGCGCAC CAGGTCA GCG  
 GTCTCGCACG ACTGGGTCGG CGGAAGTCAC TCACCGCGTG GTCCAGT CCG

Y  
N  
S  
G  
T  
N  
S  
S  
C  
C  
C  
C  
C

HS  
S  
S  
B

~~~~~  
TGTGACCATC TCGTGTAGCG GCAGCAGCAG CAACATTGGC AGCAACTATG  
ACACTGGTAG AGCACATCGC CGTCGTCGTC GTTGTAACCG TCGTTGATAC

V S W Y Q Q Q L P G T A P K L L I Y  
KpnI XmaI BbeI

~~~~~  
TGAGCTGGTA CCAGCAGTTG CCCGGGACGG CGCCGAAACT GCTGATTTAT  
ACTCGACCAT GTCTGTC AAC GGGCCCTGCC GCGGCTTTGA CGACTAAATA

D N N Q R P S G V P D R F S G S K  
Bs u36I BamHI

22

2  
2  
2  
2  
2  
2  
2

Figure 4A: V lambda 1 (Vλ1) gene sequence (continued)

```

GATAACAACC AGCGTCCCTC AGGCGTGCCG GATCGTTTAA GCGGATCCAA
CTATTGTTGG TCGCAGGGAG TCCGCACGGC CTAGCAAAAT CGCCTAGGTT

      S  G  T      S  A  S  L  A  I  T      G  L  Q      S  E  D
                                     BbsI
AAGCGGCACC AGCGCGAGCC TTGCGATTAC GGGCCTGCAA AGCGAAGACG
TTCGCCGTGG TCGCGCTCGG AACGCTAATG CCCGACGTT TCGCTTCTGC
      E  A  D  Y      Y  C  Q      Q  H  Y  T      T  P  P      V  F  G
AAGCGGATTA TTATTGCCAG CAGCATTTATA CCACCCCGCC TGTGTTTGGC
TTCGCCCTAAT AATAACGGTC GTCGTAATAT GTGGGGCGG ACACAAACCG

      G  G  T  K      L  T  V      L  G
                                     HpaI      MscI
      ~~~~~
GGCGGCACGA AGTTAACCGT TCTTGGC
CCGCCGTGCT TCAATTGGCA AGAACCG

```

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Q S A L T Q P A S V S G S P G Q S  
SexAI  
~~~~~  
CAGAGCGCAC TGACCCAGCC AGCTTCAGTG AGCGGCTCAC CAGGTCAGAG  
GTCTCGCGTG ACTGGGTCGG TCGAAGTCAC TCGCCGAGTG GTCCAGTCTC  
Eco57I  
~~~~~

|            |            |            |            |            |            |   |        |   |   |   |   |   |   |   |       |   |  |
|------------|------------|------------|------------|------------|------------|---|--------|---|---|---|---|---|---|---|-------|---|--|
| I          | T          | I          | S          | C          | T          | G | T      | S | S | D | V | G | Y | N |       |   |  |
| BssSI      |            |            |            |            |            |   |        |   |   |   |   |   |   |   |       |   |  |
| ~~~~~      |            |            |            |            |            |   |        |   |   |   |   |   |   |   |       |   |  |
| CATTACCATC | TCGTGTACGG | GTACTAGCAG | CGATGTGGGC | GGCTATAACT |            |   |        |   |   |   |   |   |   |   |       |   |  |
| GTAATGGTAG | AGCACATGCC | CATGATCGTC | GCTACACCCG | CCGATATTGA |            |   |        |   |   |   |   |   |   |   |       |   |  |
| Y          | V          | S          | W          | Y          | Q          | Q | H      | P | G | K | A | P | K | L |       |   |  |
|            |            |            |            |            |            |   | KpnI   |   |   |   |   |   |   |   | M     | I |  |
|            |            |            |            |            |            |   | XmaI   |   |   |   |   |   |   |   | BbeI  |   |  |
|            |            |            |            |            |            |   | ~~~~~  |   |   |   |   |   |   |   | ~~~~~ |   |  |
| ATGTGAGCTG | GTACCAGCAG | CATCCCCGGA | AGGCGCCGAA | ACTGATGATT |            |   |        |   |   |   |   |   |   |   |       |   |  |
| TACA       | CTCGAC     | CATGGTCGTC | GTAGGGCCCT | TCCGCGGCTT | TGACTACTAA |   |        |   |   |   |   |   |   |   |       |   |  |
| Y          | D          | V          | S          | N          | R          | P | S      | G | V | S | N | R | F | S |       |   |  |
|            |            |            |            |            |            |   | Bsu36I |   |   |   |   |   |   |   | G     | S |  |
|            |            |            |            |            |            |   | ~~~~~  |   |   |   |   |   |   |   | BamHI |   |  |
| TATGATGTGA | GCAACCGTCC | CTCAGGCGTG | AGCAACCGTT | TTAGCGGATC |            |   |        |   |   |   |   |   |   |   |       |   |  |
| ATACTA     | CACT       | CGTTGGCAGG | GAGTCCGCAC | TCGTTGGCAA | AATCGCCTAG |   |        |   |   |   |   |   |   |   |       |   |  |

Figure 4B: V lambda 2 (Vλ2) gene sequence (continued)

|           |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
|-----------|---|---|---|---|---|---|---|---|---|------|---|---|---|---|---|
| K         | S | G | N | T | A | S | L | T | I | S    | G | L | Q | A | E |
| BamHI     |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
| ~         |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
| C         | A | A | A | G | C | G | C | G | A | G    | C | C | G | A | G |
| G         | T | T | T | C | G | C | G | T | G | T    | G | A | C | C | A |
| BbsI      |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
| ~         |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
| A         | C | G | A | A | G | C | G | G | A | T    | T | A | T | T | G |
| T         | G | C | T | T | C | G | C | C | T | A    | A | T | A | A | C |
| HpaI      |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
| ~         |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
| G         | G | G | T | K | L | T | V | L | G |      |   |   |   |   |   |
|           |   |   |   |   |   |   |   |   |   | MscI |   |   |   |   |   |
| ~         |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |
| G         | G | G | C | G | G | C | A | G | T | T    | A | A | C | G | G |
| C         | C | G | C | G | C | C | G | T | T | C    | A | A | T | T | G |
| GCAAGAACC |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |

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Figure 4C: V lambda 3 (Vλ3) gene sequence

|  |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
|--|------------|------------|------------|------------|---|---|---|---|---|---|---|---|---|---|---|---|
| S  | Y          | E          | L          | T          | Q | P | P | S | V | S | V | A | P | G | Q | T |
| SexAI  |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~  |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| AGCTATGAAC   | TGACCCAGCC | GCCTTCAGTG | AGCGTTGCAC | CAGGTCAGAC |   |   |   |   |   |   |   |   |   |   |   |   |
| TCGATACTTG   | ACTGGGTCGG | CGGAAGTCAC | TCGCAACGTG | GTCCAGTCTG |   |   |   |   |   |   |   |   |   |   |   |   |
| Eco57I   |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~  |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| A  | R          | I          | S          | C          | S | G | D | A | L | G | D | K | Y | A | S |   |
| BssSI  |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~  |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| CGCGCGTATC   | TCGTGTAGCG | GGATGCGGCT | GGCGATAAA  | TACGCGAGCT |   |   |   |   |   |   |   |   |   |   |   |   |
| GC CGCATAG   | AGCACATCGC | CGCTACGCCA | CCCGCTATT  | ATGCGCTCGA |   |   |   |   |   |   |   |   |   |   |   |   |
| W  | Y          | Q          | Q          | K          | P | G | Q | A | P | V | L | V | I | Y | D | D |
| KpnI                      XmaI                      BbeI |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| ~~~~~  |            |            |            |            |   |   |   |   |   |   |   |   |   |   |   |   |
| GGTACCAGCA   | GAAACCCGGG | CAGGCGCCAG | TTCTGGTGAT | TTATGATGAT |   |   |   |   |   |   |   |   |   |   |   |   |
| CCATGGTCGT   | CTTGGGCC   | GTCCGCGGTC | AAGACCACTA | AATACTACTA |   |   |   |   |   |   |   |   |   |   |   |   |

Figure 4C: V lambda 3 (Vλ3) gene sequence (continued)

```

S D R P S G I P E R F S G S N S G
      Bsu36I      BamHI
TCTGACCGTC CCTCAGGCAT CCCGGAACGC TTTAGCGGAT CCAACAGCGG
AGACTGGCAG GGAGTCCGTA GGCCTTGCG AAATCGCCTA GGTGTGCGCC

N T A T L T I S G T Q A E D E A
      BbsI
CAACACCGCG ACCCTGACCA TTAGCGGCAC TCAGGCGGAA GACGAAGCGG
GTTGTGGCGC TGGGACTGGT AATCGCCGTG AGTCCGCCTT CTGCTTCGCC

D Y Y C Q Q H Y T T P V F G G G
ATTATTATG CCAGCAGCAT TATACCACCC CGCCTGTGTT TGGCGGCGGC
TAATAATAAC GGTGTCGTA ATATGTGGG GCGGACACAA ACCGCCGCCG

T K L T V L G
      HpaI      MscI
ACGAAGTTAA CCGTTCTTGG C
TGCTCAATT GGCAAGAACC G

```

Figure 5A: V heavy chain 1A (VH1A) gene sequence

```

Q V Q L V Q S G A E V K K P G S S
MfeI
~~~~~
CAGGTGCAAT TGGTTCAGTC TGGCCGGGAA GTGAAAAAAC CGGGCAGCAG
GTCCACGTTA ACCAAGTCAG ACCGCGCCTT CACTTTTTCG GCCCGTCGTC
V K V S C K A S G G T F S S Y A
BspEI
~~~~~
CGTGAAAGTG AGCTGCAAAG CCTCCGGAGG CACTTTTAGC AGCTATGCCG
GCACTTTCAC TCGACGTTTC GGAGGCCTCC GTGAAAATCG TCGATACGCT
I S W V R Q A P G Q G L E W M G G
BstXI
~~~~~
TTCAGTGGT GCGCAAGCC CCTGGCAGG GTCTCGAGTG GATGGCGGC
AATCGACCCA CGCGGTTCCG GGACCCGTCC CAGAGCTCAC CTACCCGCCG
I I P I F G T A N Y A Q K F Q G R
ATTATTCCGA TTTTGGCAC GGCGAACTAC GCGCAGAAAGT TTCAGGGCCG
TAATAAGGCT AAAAACCGTG CCGCTTGATG CGCGTCTTCA AAGTCCCGGC
V T I T A D E S T S T A Y M E L
BstEII

```

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Figure 5A: V heavy chain 1A (VH1A) gene sequence (continued)

```

~~~~~
GGTGACCATT ACCGCGGATG AAAGCACCAG CACCGCGTAT ATGGAACCTGA
C CACTGGTAA TGGCGCCTAC TTTCGTGGTC GTGGCGCATA TACCTTGACT

S S L R S E D T A V Y Y C A R W G
      EaqI      BssHII
      ~~~~~
GCAGCCTGCG TAGCGAAGAT ACGGCCGTGT ATTATTGCGC GCGTTGGGGC
C GTCGGACGC ATCGCTTCTA TGCCGGGCACA TAATAACGCG CGCAACCCCG

G D G F Y A M D Y W G Q G T L V T
      StyI
      ~~~~~
GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCGT GGGACCACTG

V S S
      B1pI
      ~~~~~
GGTTAGCTCA G
CCAATCGAGT C

```

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Figure 5B: V heavy chain 1B (VH1B) gene sequence

```

Q V Q L V Q S G A E V K K P G A S
MfeI
-----
CAGGTGCAAT TGGTTCAGAG CGGCGCGGAA GTGAAAAAAC CGGCGCGGAG
GTCCACGTTA ACCAAGTCTC GCCGCGCCTT CACTTTTGTG GCCCGCGCTC

V K V S C K A S G Y T F T S Y Y
BspEI
-----
CGTGAAAGTG AGCTGCAAAG CCTCCGGATA TACCTTTACC AGCTATTATA
GCACTTTCAC TCGACGTTTC GGAGGCCCTAT ATGGAATGG TCGATAATAT

M H W V R Q A P G Q G L E W M G W
BstXI
-----
XhoI
-----
TGCAC TGGGT CCGCCAAGCC CCTGGGCAGG GTCTCGAGTG GATGGGCTGG
ACGTGACCCA GCGGTTCGG GGACCCGTCC CAGAGCTCAC CTACCCGACC

I N P N S G G T N Y A Q K F Q G R
ATTAAACCGA ATAGCGGCGG CACGAAC TAC GCGAGAAGT TTCAGGGCCG
TAATTGGCT TATCGCCGCC GTGCTTGATG CCGTCTTCA AGTCCCCGC

```

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Figure 5B: V heavy chain 1B (VH1B) gene sequence (continued)

```

V   T   M   T   R   D   T   S   I   S   T   A   Y   M   E   L
BstEII
-----
GGTGACCATG ACCCGTGATA CCAGCATTAG CACCGCGTAT ATGGAAC TGA
C CACTGGTAC TGGGCACTAT GGTCGTAATC GTGGCGCATA TACCTTGACT

S   S   L   R   S   E   D   T   A   V   Y   Y   C   A   R   W   G
          EagI
          -----
          BssHII
          -----
GCAGCCTGCG TAGCGAAGAT ACGGCCGTGT ATTATTGCGC GCGTTGGGGC
CGTCGGACGC ATCGCTTCTA TGCCGGCACA TAATAACGCG CGCAACCCCG

G   D   G   F   Y   A   M   D   Y   W   G   Q   G   T   L   V   T
          StyI
          -----

GGCGATGGCT TTTATGCGAT GGATTATTGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTTCCTG GGGACCACTG

V   S   S
    BlnI
    -----
GGTTAGCTCA G
CCAATCGAGT C

```

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Figure 5C: V heavy chain 2 (VH2) gene sequence

```

Q V Q L L K E S G P A L V K P T Q T
MfeI
~~~~~
CAGGTGCAAT TGAAGAAAG CGGCCCGGCC CTGGTGAAAC CGACCCAAAC
GTCCACGTTA ACTTCTTTC GCCGGGCCGG GACCACTTTG GCTGGGTTTG

L T L T C T F S G F S L S T S G
BspEI
~~~~~
CCTGACCCTG ACCTGTACCT TTCCGGATT TAGCCTGTCC ACGTCTGGCG
GGA CTGGAC TGGACATGGA AAAGGCCTAA ATCGACAGG TGCAGACCGC

V G V G W I R Q P P G K A L E W L
BstXI XhoI
~~~~~
TTGGCGTGGG CTGGATTCGC CAGCCGCCCTG GAAAGCCCT CGAGTGGCTG
AACCGCACCC GACCTAAGCG GTCGGCGGAC CCTTTCGGGA GCTCACCGAC

A L I D W D D D K Y Y S T S L K T
MluI
~~~~~
GCTCTGATTG ATTGGGATGA TGATAAGTAT TATAGCACCA GCCTGAAAC
CGAGACTAAC TAACCCCTACT ACTATTTCATA ATATCGTGGT CGGACTTTTG

```

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Figure 5C: V heavy chain 2 (VH2) gene sequence (continued)

```

R   L   T   I   S   K   D   T   S   K   N   Q   V   V   L   T
MluI
-----
GGGTCTGACC ATTAGCAAAG ATACTTCGAA AAATCAGGTG GTGCTGACTA
CGCAGACTGG TAATCGTTTC TATGAAGCTT TTAGTCCAC CACGACTGAT

M   T   N   M   D   P   V   D   T   A   T   Y   Y   C   A   R   W
                                     BssHII
                                     -----
TGACCAACAT GGACCCGGTG GATACGGCCA CCTATTATTG CGGCGTGG
ACTGGTTGTA CCTGGGCCAC CTATGCCGGT GGATAATAAC GCGCGCAACC

G   G   D   G   F   Y   A   M   D   Y   W   G   Q   G   T   L   V
                                     StyI
                                     -----
GGCGGCGATG GCTTTATGC GATGGATTAT TGGGGCCCAAG GCACCCTGGT
CCGCCGCTAC CGAAATACG CTACCTAATA ACCCCGGTTC CGTGGGACCA

T   V   S   S
      BlnI
      -----
GACGGTTAGC TCAG
CTGCCAATCG AGTC

```

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Figure 5D: V heavy chain 3 (VH3) gene sequence

```

E V Q L V E S G G G L V Q P G G S
MfeI
-----
GAAGTGAAT TGGTGAAAG CGGCGCGGC CTGGTGCAAC CGGCGGCGCAG
CTTCACGTTA ACCACCTTC GCCGCGCGCG GACCACGTTG GCCCGCCGTC

L R L S C A A S G F T F S S Y A
BspEI
-----
CCTGCGTCTG AGCTGCGCGG CCTCCGGATT TACCTTTAGC AGCTATGCCA
GGACGCAGAC TCGACGCGCC GGAGGCCCTAA ATGGAAATCG TCGATACGCT

M S W V R Q A P G K G L E W V S A
BstXI
-----
XhoI
-----
TGAGCTGGGT GCGCCAAGCC CCTGGGAAGG GTCTCGAGTG GGTGAGCGCG
ACTCGACCCA CGCGGTTCCG GGACCCCTCC CAGAGCTCAC CCACTCGCGC

I S G S G S T Y Y A D S V K G R
ATTAGCGTA GCGCGGCAG CACCTATTAT GCGGATAGCG TGAAGGCCCG
TAATCGCCAT CGCCGCCGTC GTGGATAATA CGCTATCGC ACTTCCGGC

```

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|            |   |   |             |   |             |   |             |   |             |   |        |   |   |   |   |  |
|------------|---|---|-------------|---|-------------|---|-------------|---|-------------|---|--------|---|---|---|---|--|
| F          | T | I | S           | R | D           | N | S           | K | N           | T | L      | Y | L | Q | M |  |
|            |   |   | PmlI        |   |             |   | NspV        |   |             |   |        |   |   |   |   |  |
| TTTTACCATT |   |   | TCACGTGATA  |   | ATTCGAAAAA  |   | CACCCCTGTAT |   | CTGCAAAATGA |   |        |   |   |   |   |  |
| AAAATGGTAA |   |   | AGTGCACTAT  |   | TAAGCTTTT   |   | GTGGGACATA  |   | GACGTTTACT  |   |        |   |   |   |   |  |
| N          | S | L | R           | A | E           | D | T           | A | V           | Y | Y      | C | A | R | W |  |
|            |   |   |             |   |             |   | EagI        |   |             |   | BssHII |   |   |   |   |  |
| ACAGCCTGCG |   |   | TGC GGAAGAT |   | ACG GCGGTGT |   | ATTATGCGC   |   | GCGTTGGGCG  |   |        |   |   |   |   |  |
| TGTCGGACGC |   |   | ACGCCTTCTA  |   | TGCCGGCACA  |   | TAAATAACGC  |   | CGCAACCCCG  |   |        |   |   |   |   |  |
| G          | D | G | F           | Y | A           | M | D           | Y | W           | G | Q      | G | T | L | V |  |
|            |   |   |             |   |             |   |             |   |             |   | StyI   |   |   |   |   |  |
| GGCGATGGCT |   |   | TTTATGCCGAT |   | GGATTATTGG  |   | GGCCAAGGCA  |   | CCCTGGTGAC  |   |        |   |   |   |   |  |
| CCGCTACCGA |   |   | AAATACGCTA  |   | CCTAATAACC  |   | CCGGTCCGT   |   | GGGACCACTG  |   |        |   |   |   |   |  |
| V          | S | S |             |   |             |   |             |   |             |   |        |   |   |   |   |  |
|            |   |   | BlpI        |   |             |   |             |   |             |   |        |   |   |   |   |  |
| GGTTAGCTCA |   |   | G           |   |             |   |             |   |             |   |        |   |   |   |   |  |
| CCAATCGAGT |   |   | C           |   |             |   |             |   |             |   |        |   |   |   |   |  |

Figure 5E: V heavy chain 4 (VH4) gene sequence

```

Q  V  Q  L  Q  E  S  G  P  G  L  V  K  P  S  E  T
      MfeI
-----
CAGGTGCAAT TGCAAGAAAG TGGTCCGGGC CTGGTGAAC CGAGCGAAAC
GTCCACGTTA ACGTCTTTC ACCAGGCCCG GACCACTTTG GCTCGCTTTG

L  S  L  T  C  T  V  S  G  G  S  I  S  S  Y  Y
      BspEI
-----
CCTGAGCCTG ACCTGCACCG TTTCGGGAGG CAGCATTAGC AGCTATTATT
GGA CTGGAC TGGACGTGGC AAAGGCCCTCC GTCGTAATCG TCGATAATAA

W  S  W  I  R  Q  P  P  G  K  G  L  E  W  I  G  Y
      BstXI      XhoI
-----
GGAGCTGGAT TCGCCAGCCG CCTGGGAAGG GTCTCGAGTG GATTGGCTAT
CCTCGACCCTA AGCGGTCCGC GGACCCCTCC CAGAGCTCAC CTAACCGATA

I  Y  Y  S  G  S  T  N  Y  N  P  S  L  K  S  R  V
      BstEII
-----
ATTATTATA GCGGCAGCAC CAACTATAAT CCGAGCCTGA AAAGCCGGGT
TAAATAATAT CGCCGTCGTG GTTGATATTA GGCTCGGACT TTTCGGCCCA

```

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Figure 5E: V heavy chain 4 (VH4) gene sequence (continued)

```

      T I S V D T S K N Q F S L K L S
      BstEII
      ----
      GACCAATTAGC GTTGATACTT CGAAAAACCA GTTAGCCTG AACTGAGCA
      CTGGTAATCG CAACTATGAA GCTTTTGGT CAAATCGGAC TTTGACTCGT

      S V T A A D T A V Y Y C A R W G G
              EagI
              ----
      GCGTGACGGC GCGGATACG GCCGTGTATT ATTGCGCGCG TTGGGGCGGC
      CGCACTGCCG CCGCCTATGC CGGCACATAA TAACGCGCGC AACCCGCCG

      D G F Y A M D Y W G Q G T L V T V
              StyI
              ----
      GATGGCTTTT ATCGGATGGA TTATTGGGC CAAGGCACCC TGGTGACGGT
      CTACCGAAAA TACGCTACCT AATAACCCCG GTTCCGTGGG ACCACTGCCA

      S S
      BspI
      ----
      TAGCTCAG
      ATCGAGTC

```

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Figure 5F: V heavy chain 5 (VH5) gene sequence

```

E V Q L V Q S G A E V K K P G E S
MfeI
~~~~~
GAAGTGCAAT TGGTTCAGAG CGGCGCGGAA GTGAAAAAAC CGGGCGAAAG
CTTCACGTTA ACCAAGTCTC GCCGGCCCTT CACTTTTTCG GCCCGCTTC

L K I S C K G S G Y S F T S Y W
BspEI
~~~~~
CCTGAAAATT AGCTGCAAAG GTTCCGGGATA TTCCTTTACG AGCTATTGGA
GGACTTTTAA TCGACGTTTC CAAGGCCCTAT AAGGAAATGC TCGATAACCT

I G W V R Q M P G K G L E W M G I
BstXI XhoI
~~~~~
TTGGCTGGGT GCGCCAGATG CCTGGGAAGG GTCTCGAGTG GATGGGCATT
AACCGACCCA CGCGGTCTAC GGACCCCTCC CAGAGCTCAC CTACCCGTAA

I Y P G D S D T R Y S P S F Q G Q
ATTATCCGG GCGATAGCGA TACCCGTTAT TCTCCGAGCT TTCAGGGCCA
TAAATAGGCC CGCTATCGCT ATGGGCAATA AGAGGCTCGA AAGTCCCGGT

```

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Figure 5F: V heavy chain 5 (VH5) gene sequence (continued)

```

V   T   I   S   A   D   K   S   I   S   T   A   Y   L   Q   W
BstEII
~~~~~
GGTGACCAATT AGCGCGGATA AAAGCATTAG CACCGCGTAT CTCAATGGA
CCTACTGGTAA TCGCGCCTAT TTTCGTAATC GTGGCGCATA GAAGTTACCT

S   S   L   K   A   S   D   T   A   M   Y   Y   C   A   R   W   G
                                     BssHII
GCAGCCTGAA AGCGAGCGAT ACGGCCATGT ATTATTGCGC GCGTTGGGGC
CGTCGGACTT TCGCTCGCTA TGCCGGTACA TAATAACGCG CGCAACCCCG

G   D   G   F   Y   A   M   D   Y   W   G   Q   G   T   L   V   T
                                     StyI
GGCGATGGCT TTTATGCGAT GGATTATGG GGCCAAGGCA CCCTGGTGAC
CCGCTACCGA AAATACGCTA CCTAATAACC CCGGTCCGT GGGACCACTG

V   S   S
      BlnI
      ~~~~~
GGTTAGCTCA G
CCAATCGAGT C

```

Figure 5G: V heavy chain 6 (VH6) gene sequence

```

Q V Q L Q Q Q S G P G L V K P S Q T
MfeI
~~~~~
CAGGTGCAAT TGCACACAGTC TGGTCCGGGC CTGGTGAAAC CGAGCCAAAC
GTCACGTTA ACGTTGTCAG ACCAGGCCCG GACCACTTTG GTCGGTTTG

L S L T C A I S G D S V S S N S
BspEI
~~~~~
CCTGAGCCTG ACCTGTGCGA TTTCGGGAGA TAGCGTGAGC AGCAACAGCG
GGA CTGGAC TGGACACGCT AAAGGCCTCT ATCGCACTCG TCGTTGTCGC

A A W N W I R Q S P G R G L E W L
BstXI
~~~~~
XhoI
~~~~~
CGGCGTGGAA CTGGATTGCG CAGTCTCCTG GGCGTGGCCT CGAGTGGCTG
GCCGCACCTT GACCTAAGCG GTCAGAGGAC CCGCACCGGA GCTCACCGAC

G R T Y Y R S K W Y N D Y A V S V
GGCCGTACCT ATTATCGTAG CAAATGGTAT AACGATTATG CCGTGAGCGT
CCGGCATGGA TAATAGCATC GTTACCATA TTGCTAATAC GCCACTCGCA

```

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Figure 5G: V heavy chain 6 (VH6) gene sequence (continued)

|                                   |   |   |   |   |   |   |   |   |   |                       |   |   |   |   |   |
|-----------------------------------|---|---|---|---|---|---|---|---|---|-----------------------|---|---|---|---|---|
| K                                 | S | R | I | T | I | N | P | D | T | S                     | K | N | Q | F | S |
|                                   |   |   |   |   |   |   |   |   |   | NspV                  |   |   |   |   |   |
| GAAAAGCCGG ATTACCATCA ACCCGGATAC  |   |   |   |   |   |   |   |   |   | TTCGAAAAC CAGTTAGCC   |   |   |   |   |   |
| CTTTTCGGCC TAATGGTAGT TGGGCCTATG  |   |   |   |   |   |   |   |   |   | AAGCTTTTG GTCAAATCGG  |   |   |   |   |   |
| L                                 | Q | L | N | S | V | T | P | E | D | T                     | A | V | Y | C | A |
|                                   |   |   |   |   |   |   |   |   |   | EagI                  |   |   |   |   |   |
| TGCAACTGAA CAGCGTGACC CCGGAAGATA  |   |   |   |   |   |   |   |   |   | CGGCCGTGTA TTATTGCGCG |   |   |   |   |   |
| ACGTTGACTT GTCGCACTGG GGCCTTCTAT  |   |   |   |   |   |   |   |   |   | GCCGGCACAT AATAACGCGC |   |   |   |   |   |
| R                                 | W | G | G | D | G | F | Y | A | M | D                     | Y | W | G | Q | G |
| BSSHII                            |   |   |   |   |   |   |   |   |   | StyI                  |   |   |   |   |   |
| CGTTGGGGCG GCGATGGGCTT TTATGCGATG |   |   |   |   |   |   |   |   |   | GATTATTGGG GCCAAGGCAC |   |   |   |   |   |
| GCAACCCCGC CGTACCGAA AATACGCTAC   |   |   |   |   |   |   |   |   |   | CTAATAACCC CGGTTCCGTG |   |   |   |   |   |
| L                                 | V | T | V | S | S |   |   |   |   |                       |   |   |   |   |   |
|                                   |   |   |   |   |   |   |   |   |   | BlpI                  |   |   |   |   |   |
| CCTGGTGACG GTTAGCTCAG             |   |   |   |   |   |   |   |   |   | ~~~~~                 |   |   |   |   |   |
| GGACCACTGC CAATCGAGTC             |   |   |   |   |   |   |   |   |   |                       |   |   |   |   |   |

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Figure 6: oligonucleotides for gene synthesis

**O1K1** 5' - GAATGCATACGCTGATATCCAGATGACCCAGAG-  
CCCGTCTAGCCTGAGC -3'

**O1K2** 5' - CGCTCTGCAGGTAATGGTCACACGATCACCCAC-  
GCTCGCGCTCAGGCTAGACGGGC -3'

**O1K3** 5' - GACCATTACCTGCAGAGCGAGCCAGGGCATTAG-  
CAGCTATCTGGCGTGGTACCAGCAG -3'

**O1K4** 5' - CTTTGCAAGCTGCTGGCTGCATAAATTAATAGT-  
TTCGGTGCTTTACCTGGTTTCTGCTGGTACCACGCCAG -3'

**O1K5** 5' - CAGCCAGCAGCTTGCAAAGCGGGGTCCCGTCCC-  
GTTTTAGCGGCTCTGGATCCGGCACTGATTTTAC -3'

**O1K6** 5' - GATAATAGGTCGCAAAGTCTTCAGGTTGCAGGC-  
TGCTAATGGTCAGGGTAAAATCAGTGCCGGATCC -3'

**O2K1** 5' - CGATATCGTGATGACCCAGAGCCCACTGAGCCT-  
GCCAGTGACTCCGGGCGAGCC -3'

**O2K2** 5' - GCCGTTGCTATGCAGCAGGCTTTGGCTGCTTCT-  
GCAGCTAATGCTCGCAGGCTCGCCCGGAGTCAC -3'

**O2K3** 5' - CTGCTGCATAGCAACGGCTATAACTATCTGGAT-  
TGGTACCTTCAAAAACCAGGTCAAAGCCC -3'

**O2K4** 5' - CGATCCGGGACCCCACTGGCACGGTTGCTGCCC-  
AGATAAATTAATAGCTGCGGGCTTTGACCTGGTTTTTG -3'

**O2K5** 5' - AGTGGGGTCCCGGATCGTTTTAGCGGCTCTGGA-  
TCCGGCACCGATTTTACCCTGAAAATTAGCCGTGTG -3'

**O2K6** 5' - CCATGCAATAATACACGCCACGTCTTCAGCTT-  
CCACACGGCTAATTTTCAGGG -3'

**O3K1** 5' - GAATGCATACGCTGATATCGTGCTGACCCAGAG-  
CCCGG -3'

**O3K2** 5' - CGCTCTGCAGCTCAGGGTCGCACGTTCGCCCCG-  
AGACAGGCTCAGGGTCGCCGGGCTCTGGGTCAGC -3'

**O3K3** 5' - CCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCA-  
GCAGCTATCTGGCGTGGTACCAG -3'

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Figure 6: (continued)

**O3K4** 5' - GCACGGCTGCTCGCGCCATAAATTAATAGACGC-  
GGTGCTTGACCTGGTTTCTGCTGGTACCACGCCAGATAG -3'

**O3K5** 5' - GCGCGAGCAGCCGTGCAACTGGGGTCCCGGCGC-  
GTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC -3'

**O3K6** 5' - GATAATACACCGCAAAGTCTTCAGGTTCCAGGC-  
TGCTAATGGTCAGGGTAAAATCCGTGCCGGATC -3'

**O4K1** 5' - GAATGCATACGCTGATATCGTGATGACCCAGAG-  
CCCGGATAGCCTGGCG -3'

**O4K2** 5' - GCTTCTGCAGTTAATGGTCGCACGTTTCGCCAG-  
GCTCACCGCCAGGCTATCCGGGC -3'

**O4K3** 5' - CGACCATTAAC TGCAGAAGCAGCCAGAGCGTGC-  
TGTATAGCAGCAACAACAAAAC TATCTGGCGTGGTACCAG -  
3'

**O4K4** 5' - GATGCCCAATAAATTAATAGTTTCGGCGGCTGA-  
CCTGGTTTCTGCTGGTACCACGCCAGATAG -3'

**O4K5** 5' - AAAC TATTAATTTATTGGGCATCCACCCGTGAA-  
AGCGGGGTCCCGGATCGTTTTAGCGGCTCTGGATCCGGCAC -  
3'

**O4K6** 5' - GATAATACACCGCCACGTCTTCAGCTTGCAGGG-  
ACGAAATGGTCAGGGTAAAATCAGTGCCGGATCCAGAGCC -  
3'

**O1L1** 5' - GAATGCATACGCTCAGAGCGTGCTGACCCAGCC-  
GCCTTCAGTGAGTGG -3'

**O1L2** 5' - CAATGTTGCTGCTGCTGCCGCTACACGAGATGG-  
TCACACGCTGACCTGGTGCGCCACTCACTGAAGGCGGC -3'

**O1L3** 5' - GGCAGCAGCAGCAACATTGGCAGCAACTATGTG-  
AGCTGGTACCAGCAGTTGCCCCGGGAC -3'

**O1L4** 5' - CCGGCACGCCTGAGGGACGCTGGTTGTTATCAT-  
AAATCAGCAGTTTCGGCGCCGTCCCGGGCAACTGC -3'

**O1L5** 5' - CCCTCAGGCGTGCCGGATCGTTTTAGCGGATCC-  
AAAAGCGGCACCAGCGCGAGCCTTGCG -3'

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Figure 6: (continued)

O1L6 5' - CCGCTTCGTCTTCGCTTTGCAGGCCCGTAATCG-  
CAAGGCTCGCGCTGG -3'

O2L1 5' - GAATGCATACGCTCAGAGCGCACTGACCCAGCC-  
AGCTTCAGTGAGCGGC -3'

O2L2 5' - CGCTGCTAGTACCCGTACACGAGATGGTAATGC-  
TCTGACCTGGTGAGCCGCTCACTGAAGCTGG -3'

O2L3 5' - GTACGGGTACTAGCAGCGATGTGGGCGGCTATA-  
ACTATGTGAGCTGGTACCAGCAGCATCCCGG -3'

O2L4 5' - CGCCTGAGGGACGGTTGCTCACATCATAAATCA-  
TCAGTTTCGGCGCCTTCCCGGGATGCTGCTGGTAC -3'

O2L5 5' - CAACCGTCCCTCAGGCGTGAGCAACCGTTTTAG-  
CGGATCCAAAAGCGGCAACACCGCGAGCC -3'

O2L6 5' - CCGCTTCGTCTTCCGCTTGCAGGCCGCTAATGG-  
TCAGGCTCGCGGTGTTGCCG -3'

O3L1 5' - GAATGCATACGCTAGCTATGAACTGACCCAGCC-  
GCCTTCAGTGAGCG -3'

O3L2 5' - CGCCAGCGCATCGCCGCTACACGAGATACGCG-  
CGGTCTGACCTGGTGCAACGCTCACTGAAGGCGGC -3'

O3L3 5' - GCGATGCGCTGGGCGATAAATACGCGAGCTGG-  
TACCAGCAGAAACCCGGGCAGGCGC -3'

O3L4 5' - GCGTTCCGGGATGCCTGAGGGACGGTCAGAATC-  
ATCATAAATCACCAGAACTGGCGCCTGCCCCGGGTTTC -3'

O3L5 5' - CAGGCATCCCGGAACGCTTTAGCGGATCCAACA-  
GCGGCAACACCGCGACCCTGACCATTAGCGG -3'

O3L6 5' - CCGCTTCGTCTTCCGCTGAGTGCCGCTAATGG-  
TCAGGGTC -3'

O1246H1 5' - GCTCTTCACCCCTGTTACCAAAGCCCAG-  
GTGCAATTG -3'

O1AH2 5' - GGCTTTGCAGCTCACTTTCACGCTGCTGCCCCGG-  
TTTTTTCACTTCCGCGCCAGACTGAACCAATTGCACCTGGGC-  
TTTG -3'

Figure 6: (continued)

**01AH3** 5' - GAAAGTGAGCTGCAAAGCCTCCGGAGGCACTTT-  
TAGCAGCTATGCGATTAGCTGGGTGCGCCAAGCCCCTGGGCAG  
GGTC -3'

**01AH4** 5' - GCCCTGAAACTTCTGCGCGTAGTTCGCCGTGCC-  
AAAAATCGGAATAATGCCGCCCATCCACTCGAGACCCTGCCC-  
AGGGGC -3'

**01AH5** 5' - GCGCAGAAGTTTCAGGGCCGGGTGACCATTACC-  
GCGGATGAAAGCACCAGCACC GCGTATATGGAAGT GAGCAGCC  
TGCG -3'

**01ABH6** 5' - GCGCGCAATAATACACGGCCGTATCTTCGCT-  
ACGCAGGCTGCTCAGTTCC -3'

**01BH2** 5' - GGCTTTGCAGCTCACTTTCACGCTCGCGCCCGG-  
TTTTTTCACCTCCGCGCCGCTCTGAACCAATTGCACCTGGGC-  
TTTG -3'

**01BH3** 5' - GAAAGTGAGCTGCAAAGCCTCCGGATATACCTT-  
TACCAGCTATTATATGCACTGGGTCCGCCAAGCCCCTGGGCAG  
GGTC -3'

**01BH4** 5' - GCCCTGAAACTTCTGCGCGTAGTTCGTGCCGCC-  
GCTATTCGGGTTAATCCAGCCCATCCACTCGAGACCCTGCCCCA  
GGGGC -3'

**01BH5** 5' - GCGCAGAAGTTTCAGGGCCGGGTGACCATGACC-  
CGTGATACCAGCATTAGCACCGCGTATATGGAAGT GAGCAGCC  
TGCG -3'

**02H2** 5' - GGTACAGGTCAGGGTCAGGGTTTGGGTGCGTTT-  
CACCAGGGCCGGGCGCTTTCTTTCAATTGCACCTGGGCTTTG  
-3'

**02H3** 5' - CTGACCCTGACCTGTACCTTTTCCGGATTTAGC-  
CTGTCCACGTCTGGCGTTGGCGTGGGCTGGATTGCCAGCCGC  
CTGGGAAAG -3'

**02H4** 5' - GCGTTTTTCAGGCTGGTGCTATAATACTTATCAT-  
CATCCCAATCAATCAGAGCCAGCCACTCGAGGGCTTTCCCAGG  
CGGCTGG -3'

Figure 6: (continued)

**O2H5** 5' - GCACCAGCCTGAAAACGCGTCTGACCATTAGCA-  
AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACAT  
GG -3'

**O2H6** 5' - GCGCGCAATAATAGGTGGCCGTATCCACCGGGT-  
CCATGTTGGTCATAGTCAGC -3'

**O3H1** 5' - CGAAGTGCAATTGGTGGAAAGCGGCGGCGGCCT-  
GGTGCAACCGGGCGGCAG -3'

**O3H2** 5' - CATAGCTGCTAAAGGTAAATCCGGAGGCCGCGC-  
AGCTCAGACGCAGGCTGCCGCCCCGGTTGCAC -3'

**O3H3** 5' - GATTTACCTTTAGCAGCTATGCGATGAGCTGGG-  
TGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAG -3'

**O3H4** 5' - GGCCTTTCACGCTATCCGCATAATAGGTGCTGC-  
CGCCGCTACCGCTAATCGCGCTCACCCACTCGAGACCC -3'

**O3H5** 5' - CGGATAGCGTGAAAGGCCGTTTTACCATTTCAC-  
GTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAG-3'

**O3H6** 5' - CACGCGCGCAATAATACACGGCCGTATCTTCCG-  
CACGCAGGCTGTTCATTTGCAGATACAGG -3'

**O4H2** 5' - GGTCAGGCTCAGGGTTTCGCTCGGTTTCACCAG-  
GCCCCGACCCTTTCTTGCAATTGCACCTGGGCTTTG -3'

**O4H3** 5' - GAAACCCTGAGCCTGACCTGCACCGTTTCCGGA-  
GGCAGCATTAGCAGCTATTATTGGAGCTGGATTCGCCAGCCGC  
-3'

**O4H4** 5' - GATTATAGTTGGTGCTGCCGCTATAATAAATAT-  
AGCCAATCCACTCGAGACCCTTCCCAGGCGGCTGGCGAATCCA  
G -3'

**O4H5** 5' - CGGCAGCACCAACTATAATCCGAGCCTGAAAAG-  
CCGGGTGACCATTAGCGTTGATACTTCGAAAAACCAGTTTAGC  
CTG -3'

**O4H6** 5' - GCGCGCAATAATACACGGCCGTATCCGCCGCCG-  
TCACGCTGCTCAGTTTCAGGCTAAACTGGTTTTTCG -3'

Figure 6: (continued)

**O5H1** 5' - GCTCTTCACCCCTGTTACCAAAGCCGAAGTGCA-  
ATTG -3'

**O5H2** 5' - CCTTTGCAGCTAATTTTCAGGCTTTCGCCCCGGT-  
TTTTTCACTTCCGCGCCGCTCTGAACCAATTGCACTTCGGCTT  
TGG -3'

**O5H3** 5' - CCTGAAAATTAGCTGCAAAGGTTCCGGATATTC-  
CTTTACGAGCTATTGGATTGGCTGGGTGCGCCAGATGCCTGG  
-3'

**O5H4** 5' - CGGAGAATAACGGGTATCGCTATCGCCCCGGATA-  
AATAATGCCCATCCACTCGAGACCTTCCCAGGCATCTGGCGC  
AC -3'

**O5H5** 5' - CGATACCCGTTATTCTCCGAGCTTTCAGGGCCA-  
GGTGACCATTAGCGCGGATAAAAGCATTAGCACCGCGTATCTT  
C -3'

**O5H6** 5' - GCGCGCAATAATACATGGCCGTATCGCTCGCTT-  
TCAGGCTGCTCCATTGAAGATACGCGGTGCTAATG -3'

**O6H2** 5' - GAAATCGCACAGGTCAGGCTCAGGGTTTGGCTC-  
GGTTTCACCAGGCCCGGACCAGACTGTTGCAATTGCACCTGG-  
GCTTTG -3'

**O6H3** 5' - GCCTGACCTGTGCGATTTCGGGAGATAGCGTGA-  
GCAGCAACAGCGCGGCGTGGAAGTGGATTTCGCCAGTCTCCTGG  
GCG -3'

**O6H4** 5' - CACCGCATAATCGTTATACCATTTGCTACGATA-  
ATAGGTACGGCCCAGCCACTCGAGGCCACGCCCAGGAGACTG-  
GCG -3'

**O6H5** 5' - GGTATAACGATTATGCGGTGAGCGTGAAAAGCC-  
GGATTACCATCAACCCGGATACTTCGAAAAACCAGTTTAGCCT  
GC -3'

**O6H6** 5' - GCGCGCAATAATACACGGCCGTATCTTCCGGGG-  
TCACGCTGTTCAAGTTGCAGGCTAAACTGGTTTTC -3'

**OCLK1** 5' - GGCTGAAGACGTGGGCGTGTATTATTGCCAGCA-  
GCATTATACCACCCCGCCGACCTTTGGCCAGGGTAC -3'

Figure 6: (continued)

OCLK2 5' - GCGGAAAAATAAACACGCTCGGAGCAGCCACCG-  
TACGTTTAATTTCAACTTTCGTACCCTGGCCAAAGGTC -3'

OCLK3 5' - GAGCGTGTTTATTTTTCCGCCGAGCGATGAACA-  
ACTGAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTG -3'

OCLK4 5' - CAGCGCGTTGTCTACTTTCCACTGAACTTTCGC-  
TTCACGCGGATAAAAGTTGTTTCAGCAGGCACACCACGC -3'

OCLK5 5' - GAAAGTAGACAACGCGCTGCAAAGCGGCAACAG-  
CCAGGAAAGCGTGACCGAACAGGATAGCAAAGATAG -3'

OCLK6 5' - GTTTTTCATAATCCGCTTTGCTCAGGGTCAGGG-  
TGCTGCTCAGAGAATAGGTGCTATCTTTGCTATCCTGTTGC -  
3'

OCLK7 5' - GCAAAGCGGATTATGAAAAACATAAAGTGTATG-  
CGTGCGAAGTGACCCATCAAGGTCTGAGCAGCCCGGTG -3'

OCLK8 5' - GGCATGCTTATCAGGCCTCGCCACGATTAAAAG-  
ATTTAGTCACCGGGCTGCTCAGAC -3'

OCH1 5' - GGCGTCTAGAGGCCAAGGCACCCTGGTGACGGT-  
TAGCTCAGCGTCGAC -3'

OCH2 5' - GTGCTTTTGCTGCTCGGAGCCAGCGGAAACACG-  
CTTGGACCTTTGGTCGACGCTGAGCTAACC -3'

OCH3 5' - CTCCGAGCAGCAAAAGCACCAGCGGCGGCACGG-  
CTGCCCTGGGCTGCCTGGTTAAAGATTATTTCC -3'

OCH4 5' - CTGGTCAGCGCCCCGCTGTTCCAGCTCACGGTG-  
ACTGGTTCCGGGAAATAATCTTTAACCAGGCA -3'

OCH5 5' - AGCGGGGCGCTGACCAGCGGCGTGCATACCTTT-  
CCGGCGGTGCTGCAAAGCAGCGGCCTG -3'

OCH6 5' - GTGCCTAAGCTGCTGCTCGGCACGGTCACAACG-  
CTGCTCAGGCTATACAGGCCGCTGCTTTGCAG -3'

OCH7 5' - GAGCAGCAGCTTAGGCACTCAGACCTATATTTG-  
CAACGTGAACCATAAACCGAGCAACACC -3'

OCH8 5' - GCGCGAATTCGCTTTTCGGTTCCACTTTTTTAT-  
CCACTTTGGTGTTGCTCGGTTTATGG -3'

Figure 7A: sequence of the synthetic Ck gene segment

```

      V   A   A   P   S   V   F   I   F   P   P   S   D   E   Q
BsiWI
~~~~~
CGTACGGTGG CTGCTCCGAG CGTGTTTATT TTTCCGCCGA GCGATGAACA
GCATGCCACC GACGAGGCTC GCACAAATAA AAAGGCGGCT CGCTACTTGT

      L   K   S   G   T   A   S   V   V   C   L   L   N   N   F   Y
ACTGAAAAGC GGCACGGCGA GCGTGGTGTG CCTGCTGAAC AACTTTTATC
TGACTTTTCG CCGTGCCGCT CGCACACAC GACGACTTG TTGAAAATAG

      P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S   G
CGCGTGAAGC GAAAGTTCAG TGGAAAGTAG ACAACGCGCT GCAAAGCGGC
GCGCACTTCG CTTCAAGTC ACCTTTCATC TGTTCGCCGA CGTTTCGCCG

      N   S   Q   E   S   V   T   E   Q   D   S   K   D   S   T   Y   S
AACAGCCAGG AAAGCGTGAC CGAACAGGAT AGCAAAGATA GCACCTATTC
TTGTCGGTCC TTTCGCACTG GCTTGTCCTA TCGTTTCTAT CGTGGATAAG

      L   S   S   T   L   T   L   S   K   A   D   Y   E   K   H   K
TCTGAGCAGC ACCCTGACCC TGAGCAAAGC GGATTATGAA AAACATAAAG
AGACTCGTCG TGGGACTGGG ACTCGTTTCG CCTAATACTT TTTGTATTTC

```



Figure 7A: sequence of the synthetic Cx gene segment (continued)

V Y A C E V T H Q G L S S P V T K  
 TGTATGCGTG CGAAGTGACC CATCAAGGTC TGAGCAGCCC GGTGACTAAA  
 ACATACGCAC GCTTCACTGG GTAGTCCAG ACTCGTCGGG CCACTGATTT

S F N R G E A \*  
           StuI           SphI  
           ~~~~~       ~~~~~  
 TCTTTTAATC GTGGCGAGGC CTGATAAGCA TGC  
 AGAAATATAG CACCGCTCCG GACTATTCGT ACG

Figure 7B: sequence of the synthetic CH1 gene segment

```

      A  S  T  K  G  P  S  V  F  P  L  A  P  S  S
BlpI  SalI
~~~~~
GCTCAGCGTC GACCAAAGGT CCAAGCGTGT TTCCGCTGGC TCCGAGCAGC
CGAGTCGCAG CTGGTTTCCA GGTTCGCACA AAGCGACCG AGGCTCGTCG

      K  S  T  S  G  G  T  A  A  L  G  C  L  V  K  D  Y
AAAGCACCA GCGCGGCAC GGCTGCCCTG GGCTGCCCTGG TTAAGATTA
TTTTCGTGGT CGCCGCCGTG CCGACGGGAC CCGACGGACC AATTCTAAT

      F  P  E  P  V  T  V  S  W  N  S  G  A  L  T  S
TTTCCCGGAA CCAGTCACCG TGAGCTGGAA CAGCGGGGCG CTGACCAGCG
AAAGGCGCTT GGTCAGTGGC ACTCGACCTT GTCGCCCCGC GACTGGTCGC

      G  V  H  T  F  P  A  V  L  Q  S  S  G  L  Y  S  L
GCGTGCATAC CTTTCCGGCG GTGCTGCAAA GCAGCGGCCT GTATAGCCTG
CGCACGTATG GAAAGGCCCG CACGACGTTT CGTCGCCCGA CATATCGGAC

      S  S  V  V  T  V  P  S  S  S  L  G  T  Q  T  Y  I
AGCAGCGTTG TGACCGTGCC GAGCAGCAGC TTAGGCACTC AGACCTATAT
TCGTCCGAAC ACTGGCACGG CTCGTCGTCG AATCCGTGAG TCTGGATATA

```

Figure 7B; sequence of the synthetic CH1 gene segment (continued)

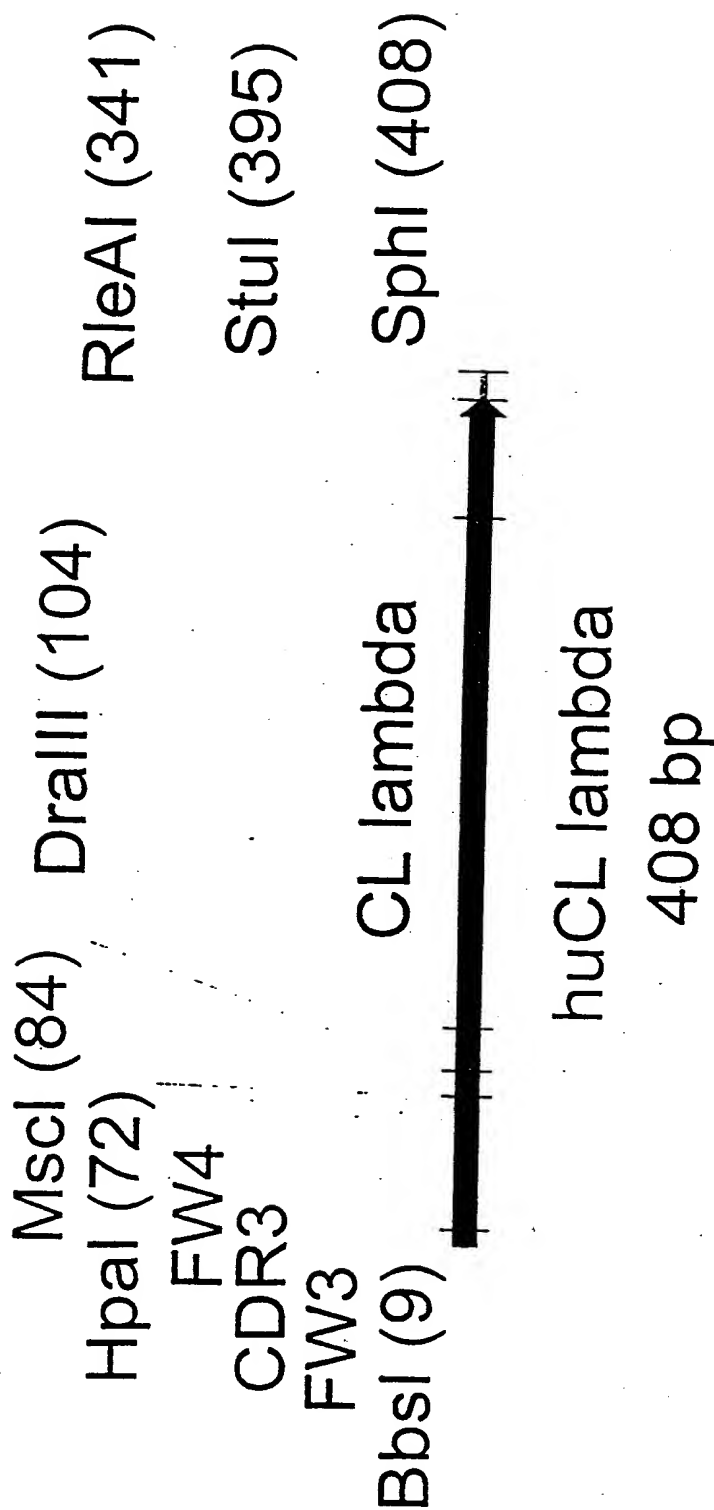
|            |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
|------------|------------|------------|-------------|------------|---|---|---|---|---|---|---|---|---|---|---|
| C          | N          | V          | N           | H          | K | P | S | N | T | K | V | D | K | K | V |
| TTGCAACGTG | AACCATAAAC | CGAGCAACAC | CAAAGTGGAT  | AAAAAAGTGG |   |   |   |   |   |   |   |   |   |   |   |
| AACGTTGCAC | TTGGTATTG  | GCTCGTTGTG | GTTTACACCTA | TTTTTTCACC |   |   |   |   |   |   |   |   |   |   |   |

|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| E | P | K | S | E | F | * |
|---|---|---|---|---|---|---|

|       |         |
|-------|---------|
| ECORI | HindIII |
| ~~~~~ | ~~~~~   |

|            |            |         |
|------------|------------|---------|
| AACCGAAAAG | CGAATTCTGA | TAAGCTT |
| TTGGCTTTC  | GCTTAAGACT | ATTCGAA |

Figure 7C: functional map and sequence of module 24 comprising the synthetic CA gene segment (huCL lambda)



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Figure 7C: functional map and sequence of module 24 comprising the synthetic CI gene segment (huCL lambda) (continued)

| BbsI   |             | HpaI        |            | MscI       |             | DraIII |  |
|--------|-------------|-------------|------------|------------|-------------|--------|--|
| ~~~~~  |             | ~~~~~       |            | ~~~~~      |             | ~~~~~  |  |
| 1      | GAAGACGAAG  | CGGATTATTA  | TTGCCAGCAG | CATTATACCA | CCCCGCCCTGT |        |  |
|        | CTTCTGCTTC  | GCCTAATAAT  | AACGGTCGTC | GTAATATGTT | GGGGCGGACA  |        |  |
| 51     | GTTTGGCGGC  | GGCACGAAGT  | TAACCGTTCT | TGGCCAGCCG | AAAGCCGCAC  |        |  |
|        | CAAACCGCCG  | CCGTGCTTCA  | ATTGGCAAGA | ACCGTCGGC  | TTTCGGCGTG  |        |  |
| DraIII |             |             |            |            |             |        |  |
| ~~~~~  |             |             |            |            |             |        |  |
| 101    | CGAGTGTGAC  | GCTGTTTCCG  | CCGAGCAGCG | AAGAATTGCA | GGCGAACAAA  |        |  |
|        | GTCACACTG   | CGACAAAGC   | GGCTCGTCGC | TTCTTAACGT | CCGCTTGTTT  |        |  |
| 151    | GCGACCCCTGG | TGTGCCCTGAT | TAGCGACTTT | TATCCGGGAG | CCGTGACAGT  |        |  |
|        | CGCTGGGACC  | ACACGGACTA  | ATCGCTGAAA | ATAGGCCCTC | GGCACTGTCA  |        |  |
| 201    | GGCCTGGAAG  | GCAGATAGCA  | GCCCCGTCAA | GGCGGGAGTG | GAGACCACCA  |        |  |
|        | CCGGACCTTC  | CGTCTATCGT  | CGGGGCAGTT | CCGCCCTCAC | CTCTGGTGGT  |        |  |

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Figure 7C: functional map and sequence of module 24 comprising the synthetic CI gene segment (huCl lambda) (continued)

```
251  CACCCCTCCAA ACAAAGCAAC AACAAAGTACG CGGCCAGCAG CTATCTGAGC
      GTGGGAGGTT TGTTTCGTTG TTGTTTCATGC GCCGGTCGTC GATAGACTCG

      RleAI
      ~~~~~
301  CTGACGCCTG AGCAGTGGAA GTCCACACAGA AGCTACAGCT GCCAGGTCAC
      GACTGCGGAC TCGTCACCTT CAGGTGTCT TCGATGTCGA CGGTCCAGTG

      StuI
      ~~~~~
351  GCATGAGGGG AGCACC GTG AAAAAACCGT TGC GCCGACT GAGCCTGAT
      CGTACTCCCC TCGTGGCACC TTTT TTTGGCA ACGCGGCTGA CTCCGGACTA

      SphI
      ~~~~~
401  AAGCATGC
      TTCGTACG
```

Figure 7D: oligonucleotides used for synthesis of module M24 containing Cλ gene segment

M24: assembly PCR

M24-A: GAAGACAAGCGGATTATTATGGCCAGCAGCATTATACCAACCCGCCCTGTGTTGGCGGCG-  
GCACGAAGTTAACCGTTC

M24-B: CAATTCTTCGCTCGCTCGCGGAACAGCGTCACACTCGGTGGGCTTCGGCTGGCCAA-  
GAACGGTTAACTTCGTGCCGC

M24-C: CGCCGAGCAGCGAAGAATGCAGGCGAACAAAGCGACCCCTGGTGTGCCTGATTAGCGACT-  
TTATCCGGGAGCCGTGACA

M24-D: TGTTGGAGGGTGTGGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGCCTTCCAG-  
GCCACTGTACGGCTCCCGG

M24-E: CCACACCTCCAAACAAGCAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC-  
CTGAGCAGTGGAGTCCACAGAAGCTACAGCTG

M24-F: GCATGCTTATCAGGCCCTCAGTCGGCGCAACGGTTTTTCCACGGTGTCTCCCTCATGCGT-  
GACCTGGCAGCTGTAGCTTC

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2

```

M  K  Q  S  T  I  A  L  A  L  L  P  L  L  F  T  P
                               Sapi
ATGAAACAAA  GCACTATTGC  ACTGGCACTC  TTACCGTTGC  TCTCACCCC
TACTTTGTTT  CGTGATAACG  TGACCGTGAG  AATGGCAACG  AGAAGTGGG

V  T  K  A  D  Y  K  D  E  V  Q  L  V  E  S  G
                               MfeI
TGTACCAAAA  GCCGACTACA  AAGATGAAGT  GCAATTGGTG  GAAAGCGGCG
ACAAATGGTTT  CGGCTGATGT  TTCTACTTCA  CGTTAACAC  CTTTCGCCGC

G  G  L  V  Q  P  G  G  S  L  R  L  S  C  A  A  S
                               BspEI
GGGCCCTGGT  GCAACCGGGC  GGCAGCCTGC  GTCTGAGCTG  CGCGGCCCTCC
CGCCGGACCA  CGTTGGCCCG  CCGTCGGACG  CAGACTCGAC  GCGCCGGAGG

G  F  T  F  S  S  Y  A  M  S  W  V  R  Q  A  P  G
BspEI
GGATTACCT  TTAGCAGCTA  TGCATGAGC  TGGGTGCGCC  AAGCCCCCTGG
CCTAAATGGA  AATCGTCGAT  ACGTACTCG  ACCACGCGG  TTCGGGACC

```

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Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

|                                                         |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
|---------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|--------|-------|
| K                                                       | G | L | E | W | V | S | A | I | S | G | S | G | S      | T     |
| XhoI                                                    |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| ~~~~~                                                   |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| GAAGGGTCTC GAGTGGGTGA GCGGATTAG CCGTAGCGGC GGCAGCACCT   |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| CTTCCCAGAG CTCACCCACT CCGGCTAATC GCCATCGCCG CCGTCGTGGA  |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| Y                                                       | Y | A | D | S | V | K | G | R | F | T | I | S | R      | D N S |
|                                                         |   |   |   |   |   |   |   |   |   |   |   |   | PmlI   | NspV  |
|                                                         |   |   |   |   |   |   |   |   |   |   |   |   | ~~~~~  | ~~~~~ |
| ATTATGCGGA TAGCGTGAAA GGCCGTTTAA CCATTTCACG TGATAATTTCG |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| TAATACGCCCT ATCGCACTTT CCGGCAAAAT GGTAAGTGC ACTATTAAAGC |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| K                                                       | N | T | L | Y | L | Q | M | N | S | L | R | A | E      | D T A |
|                                                         |   |   |   |   |   |   |   |   |   |   |   |   | NspV   | EagI  |
|                                                         |   |   |   |   |   |   |   |   |   |   |   |   | ~~~~~  | ~~~~~ |
| AAAAACACCC TGTATCTGCA AATGAACAGC CTGCGTGCCG AAGATACGGC  |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| TTTTTGTTGG ACATAGACGT TTAATTGTCTG GACGCACGCC TTCTATGCCG |   |   |   |   |   |   |   |   |   |   |   |   |        |       |
| V                                                       | Y | Y | C | A | R | W | G | G | D | G | F | Y | A      | M D   |
|                                                         |   |   |   |   |   |   |   |   |   |   |   |   | EagI   |       |
|                                                         |   |   |   |   |   |   |   |   |   |   |   |   | BssHII |       |
|                                                         |   |   |   |   |   |   |   |   |   |   |   |   | ~~~~~  |       |
| CGTGTATTAT TCGCGCGCGTT GGGCGGCGCA TGGCTTTTAT GCGATGGATT |   |   |   |   |   |   |   |   |   |   |   |   |        |       |

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

```

GCACATAATA ACGCGCGCAA CCCC GCCGCT ACCGAAAATA CGCTACCTAA
Y W G Q G T L V T V S S A G G G S
          StyI
-----
ATTGGGGCCA AGGCACCCCTG GTGACGGTTA GCTCAGCGGG TGGCGGTTCT
TAACCCCGGT TCCGTGGGAC CACTGCCAAT CGAGTCGCC ACCGCCAAGA
          BlnI
-----
G G G G S G G G G G G G S D I
          EcoRV
-----
GGCGCGGGTG GGAGCGGTGG CGGTGGTTCT GCGGGTGGTG GTTCCGATAT
CCGCCGCCAC CCTCGCCACC GCCACCAAGA CCGCCACCAC CAAGGCTATA
          V M T Q S P L S L P V T P G E P
          EcoRV
          BanII
          -----
CGTGATGACC CAGAGCCCCAC TGAGCCTGCC AGTGACTCCG GCGAGCCCTG
GCACTACTGG GTCTCGGGTG ACTCGGACGG TCACTGAGGC CCGCTCGGAC
A S I S C R S S Q S L L H S N G Y
          PstI
          -----
CGAGCATTAG CTGCAGAAGC AGCCAAAGCC TGCTGCATAG CAACGGGCTAT
GCTCGTAATC GACGTCTTCG TCGGTTTCGG ACGACGTATC GTTGCCGATA

```

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Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

```

N Y L D W Y L Q K P G Q S P Q L L
      KpnI      SexAI      AseI
      -----
AACTATCTGG ATTGGTACCT TCAAAAACCA GGTCAAAGCC CGCAGCTATT
TTGATAGACC TAACCATGGA AGTTTTCGGT CCAGTTTCGG GCGTCGATAA

      I Y L G S N R A S G V P D R F S
      AseI      EcoO109I
      -----
AATTATCTG GGCAGCAACC GTGCCAGTGG GTCCCCGGAT CGTTTAGCG
TAAATAGAC CCGTCGTTGG CACGGTCACC CCAGGGCCTA GCAAATCGC

      G S G S G T D F T L K I S R V E A
      BamHI
      -----
GCTCTGGATC CGGCACCGAT TTACCCCTGA AAATTAGCCG TGTGGAAGCT
CGAGACCTAG GCCGTGGCTA AATGGGACT TTAAATCGGC ACACCTTCGA

      E D V G V Y Y C Q Q H Y T T P P T
      BbsI
      -----
GAAGACGTGG GCGTGTATTA TTGCCAGCAG CATTATACCA CCCC GCCGAC
CTTCTGCACC CGCACATAAT AACGGTCGTC GTAATATGGT GGGCGGCGTG

```

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Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued)

|             |            |            |             |     |   |   |   |   |   |   |   |   |   |
|-------------|------------|------------|-------------|-----|---|---|---|---|---|---|---|---|---|
| F           | G          | Q          | G           | T   | K | V | E | I | K | R | T | E | F |
| MSCI        |            |            |             |     |   |   |   |   |   |   |   |   |   |
| ~~~~~       |            |            |             |     |   |   |   |   |   |   |   |   |   |
| CTTTGGCCAG  | GGTACGAAAG | TTGAAATTAA | ACGTACGGAA  | TTC |   |   |   |   |   |   |   |   |   |
| GAAACCGGTC  | CCATGCTTC  | AACTTTAATT | TGCATGCCCTT | AAG |   |   |   |   |   |   |   |   |   |
| BsiWI ECORI |            |            |             |     |   |   |   |   |   |   |   |   |   |
| ~~~~~       |            |            |             |     |   |   |   |   |   |   |   |   |   |

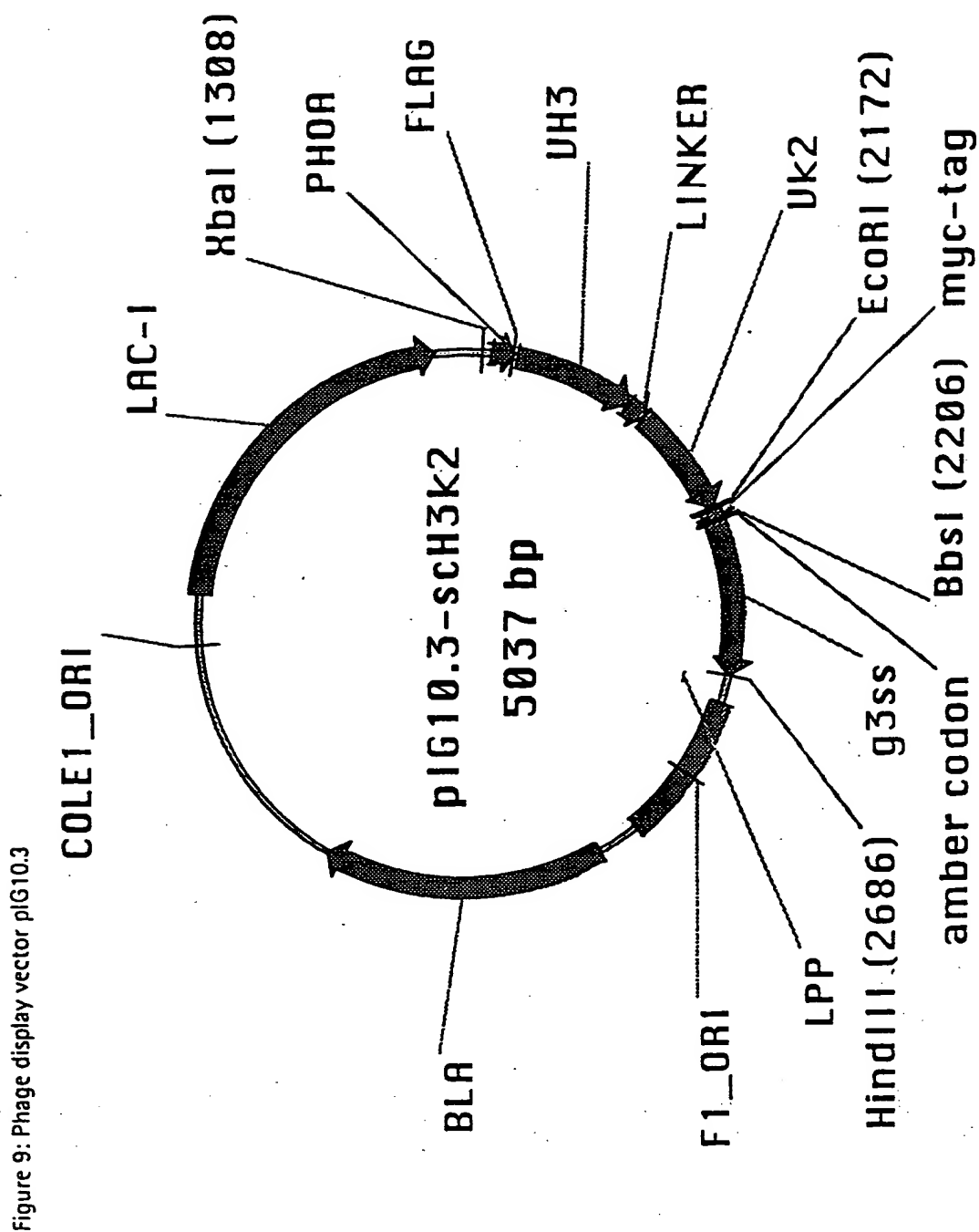


Figure 10: Sequence analysis of initial libraries

|   |      |   |   |   |   |   |   |   |   |   |   |   |   |
|---|------|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 92   | C | C | C | C | C | C | C | C | C | C | C | C |
|   | 93   | A | A | A | A | A | A | A | A | A | A | A | A |
|   | 94   | R | R | R | R | R | R | R | R | R | R | R | R |
|   | 95   | W | F | H | V | K | W | I | T | W | S | S | V |
|   | 96   | G | G | R | R | F | N | N | A | Y | V | K | A |
|   | 97   | G | K | T | E | L | T | E | I | N | G | T | P |
|   | 98   | D | M | E | L | K | T | A | T | R | D | F | Q |
|   | 99   | G | N | W | Y | A | G | Q | R | N | S | A | Y |
|   | 100  | F | Y | H | H | R | Y | P | - | S | K | A | D |
|   | 100A | Y | - | - | - | - | - | - | - | - | - | - | - |
|   | 100B | A | - | - | - | - | - | - | - | - | - | - | - |
|   | 100C | - | - | - | - | - | - | - | - | - | - | - | - |
| B | 100D | - | - | - | - | - | - | - | - | - | - | - | - |
|   | 100E | N | - | - | - | - | - | - | - | - | - | - | - |
|   | 101  | D | D | D | D | D | D | D | D | D | D | D | D |
|   | 102  | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
|   | 103  | W | W | W | W | W | W | W | W | W | W | W | W |

Figure 10: Sequence analysis of initial libraries

|   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C | C | C | C | C | C | C | C | C | C | C | C | C |
| A | A | A | A | A | A | A | A | A | A | A | A | A |
| R | R | R | R | R | R | R | R | R | R | R | R | R |
| Y | M | K | T | Y | * | R | M | K | S | Y |   |   |
| F | A | N | Q | P | G | N | K | G | W | A |   |   |
| V | L | Q | S | Y | S | P | P | S | T | G |   |   |
| H | R | M | F | R | G | W | M | E | N | T |   |   |
| F | A | V | W | S | S | N | L | F | D | T |   |   |
| L | S | F | E | N | E | V | N | L | K | F |   |   |
| Y | G | H | Q | F | H | N | R | E | P | K |   |   |
| T | K | A | Q | F | W | Y | D | T | N | Q |   |   |
| M | Y | R | K | M | S | L | G | D | F | G |   |   |
| V | I | K | V | P | I | H | T | V | I | P |   |   |
| M | M | F | M | M | F | F | M | M | M | M |   |   |
| D | D | D | D | D | D | D | D | D | D | D |   |   |
| V | V | V | Y | V | V | V | V | Y | V | Y |   |   |
| W | W | W | W | W | W | W | W | W | W | W |   |   |

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Figure 11: Expression analysis of initial library

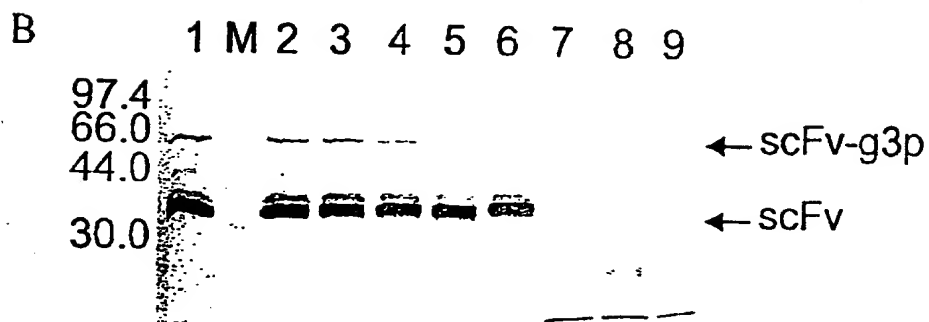
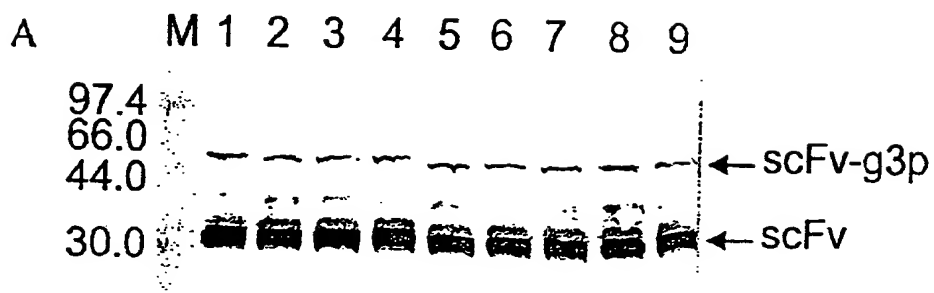




Figure 12: Increase of specificity during the panning rounds

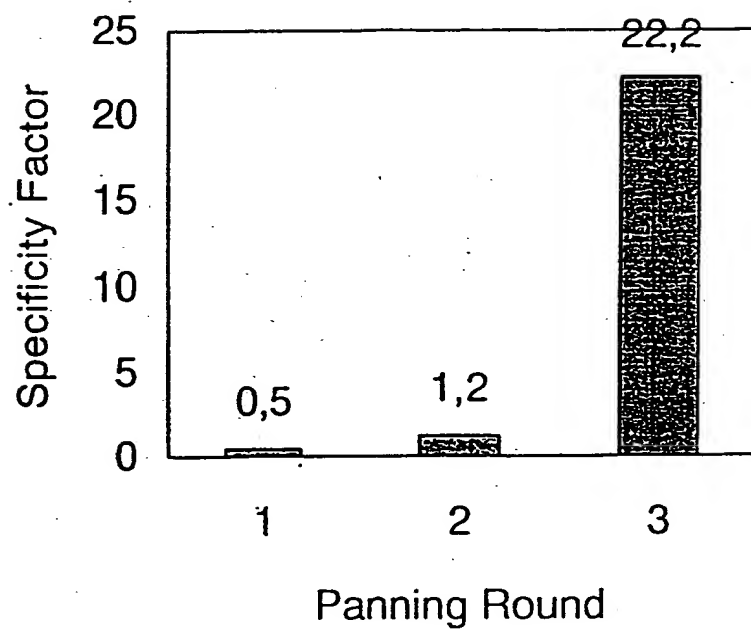


Figure 13: Phage ELISA of clones after the 3rd round of panning

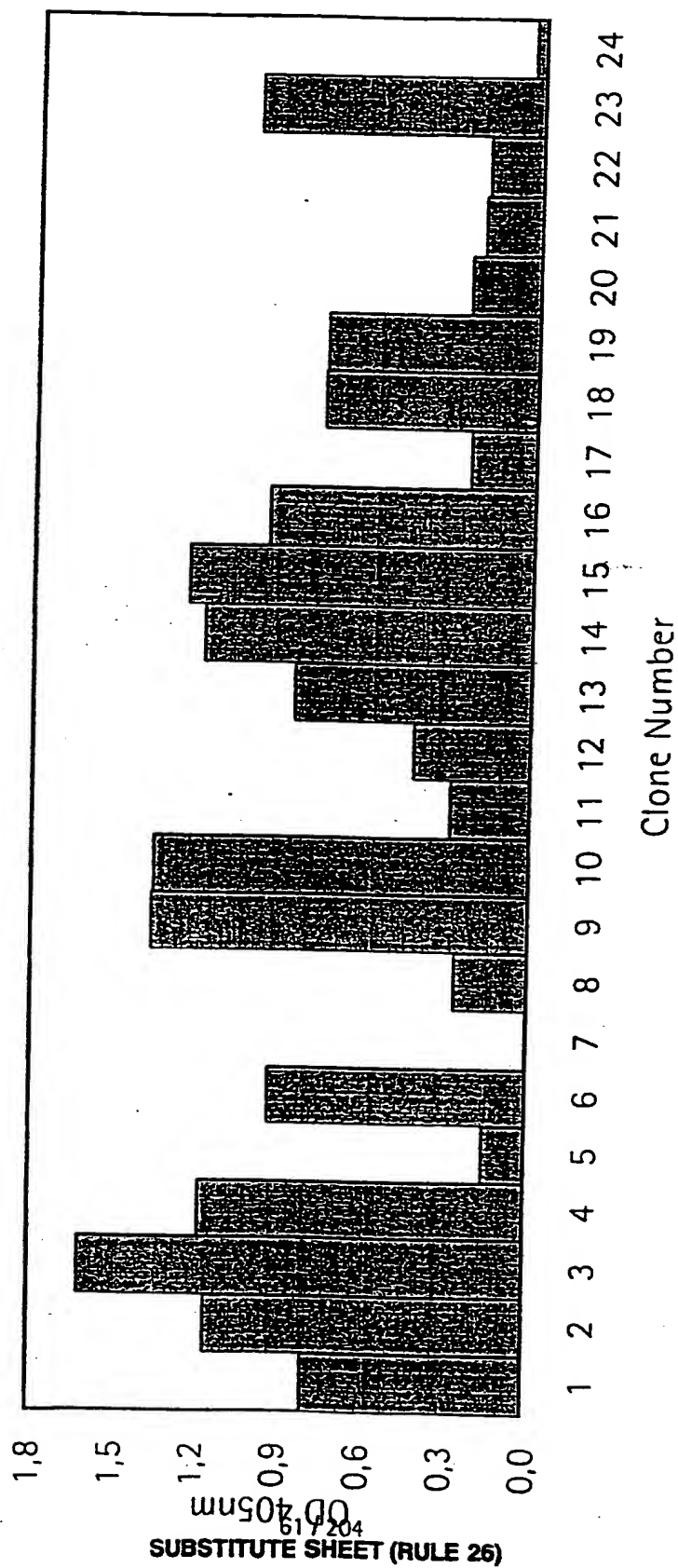
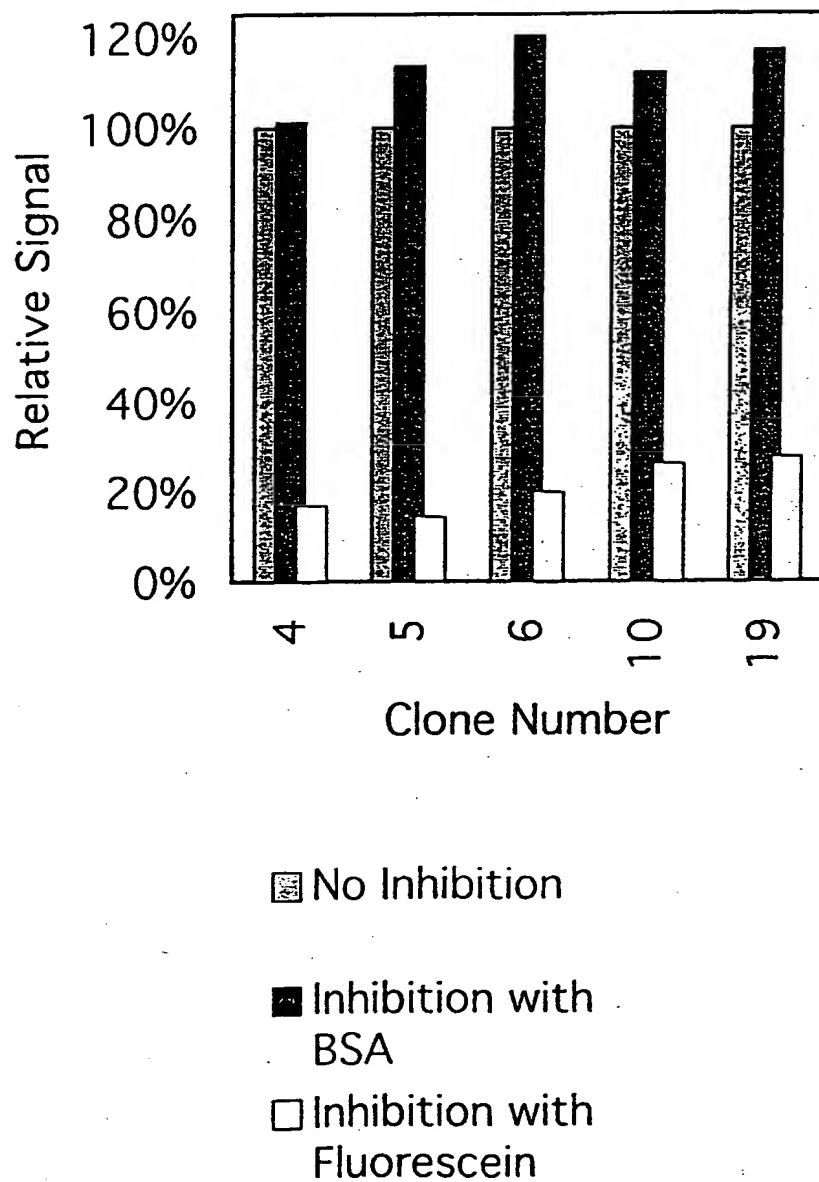
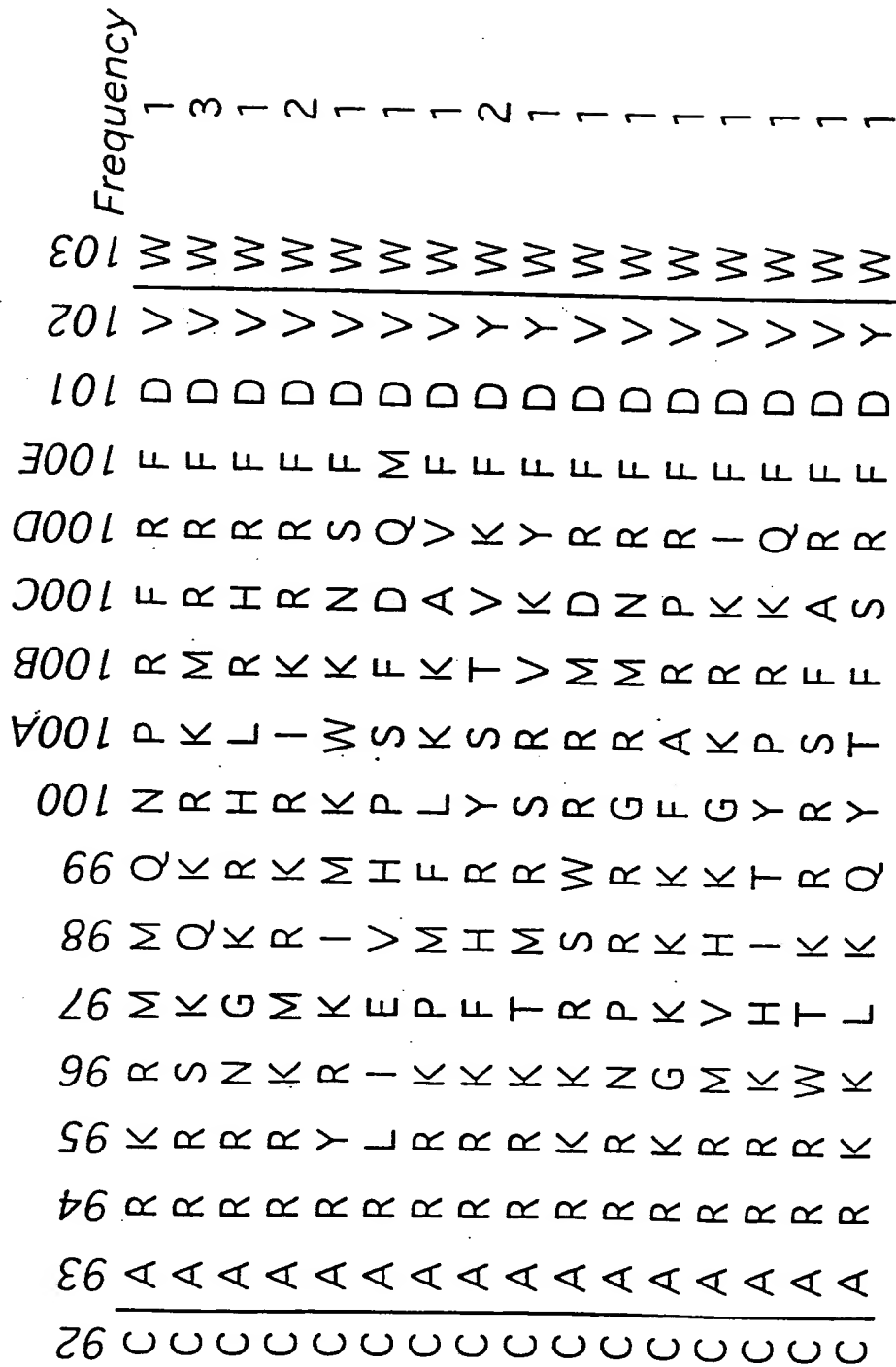


Figure 14: Competition ELISA





**Figure 15: Sequence analysis of fluorescein binders**

Figure 16: Purification of fluorescein binding scFv fragments



Figure 17: Enrichment factors after three rounds of panning

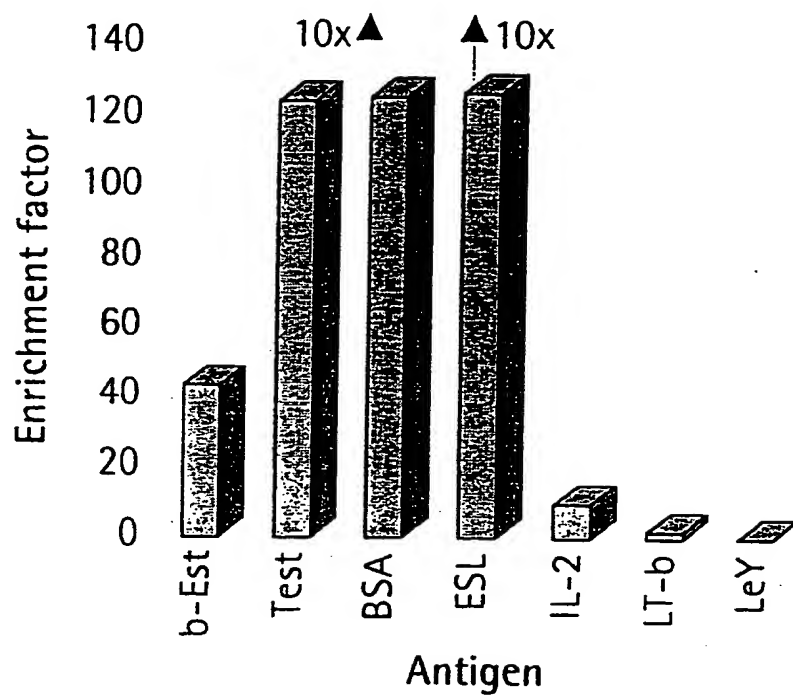


Figure 18: ELISA of anti-ESL-1 and anti- $\beta$ -estradiol antibodies

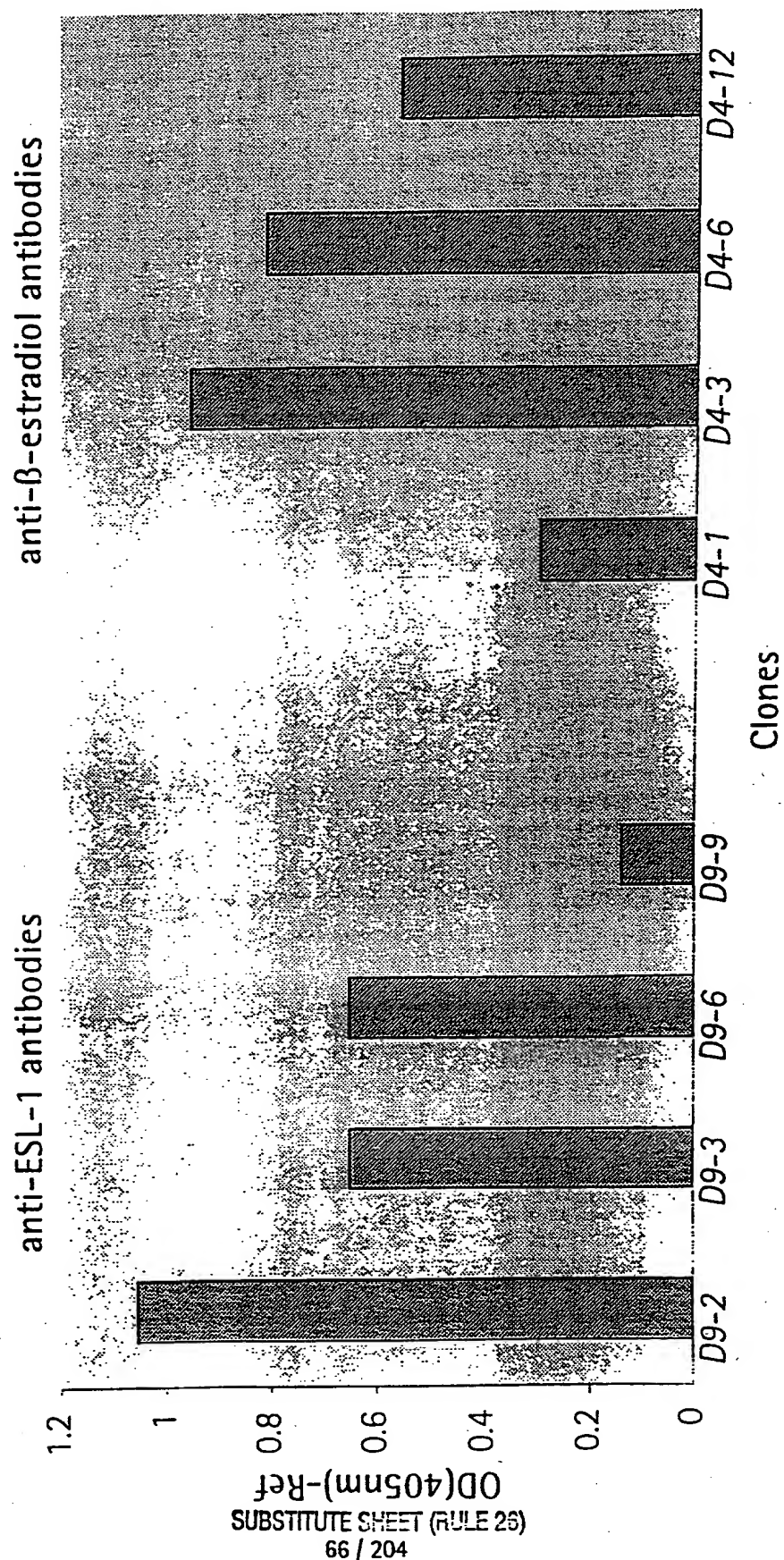


Figure 19: Selectivity and cross-reactivity of HuCAL antibodies

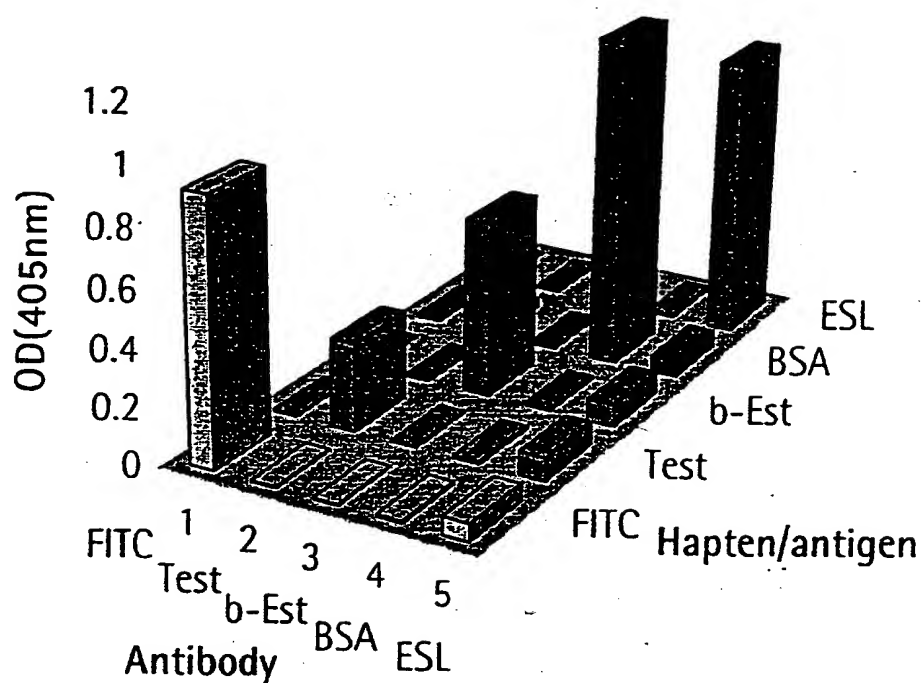




Figure 20: Sequence analysis of estradiol binders

| Frequency |        |
|-----------|--------|
| 3         | 103 W  |
| 8         | 102 V  |
| 7         | 101 D  |
| 1         | 100F F |
| 1         | 100D G |
| 1         | 100C K |
| 1         | 100B R |
| 1         | 100A T |
| 1         | 100 A  |
| 1         | 99 Q   |
| 1         | 98 W   |
| 1         | 97 P   |
| 1         | 96 R   |
| 1         | 95 T   |
| 1         | 94 R   |
| 1         | 93 A   |
| 5         | 92 C   |
| 4         |        |
| 1         |        |

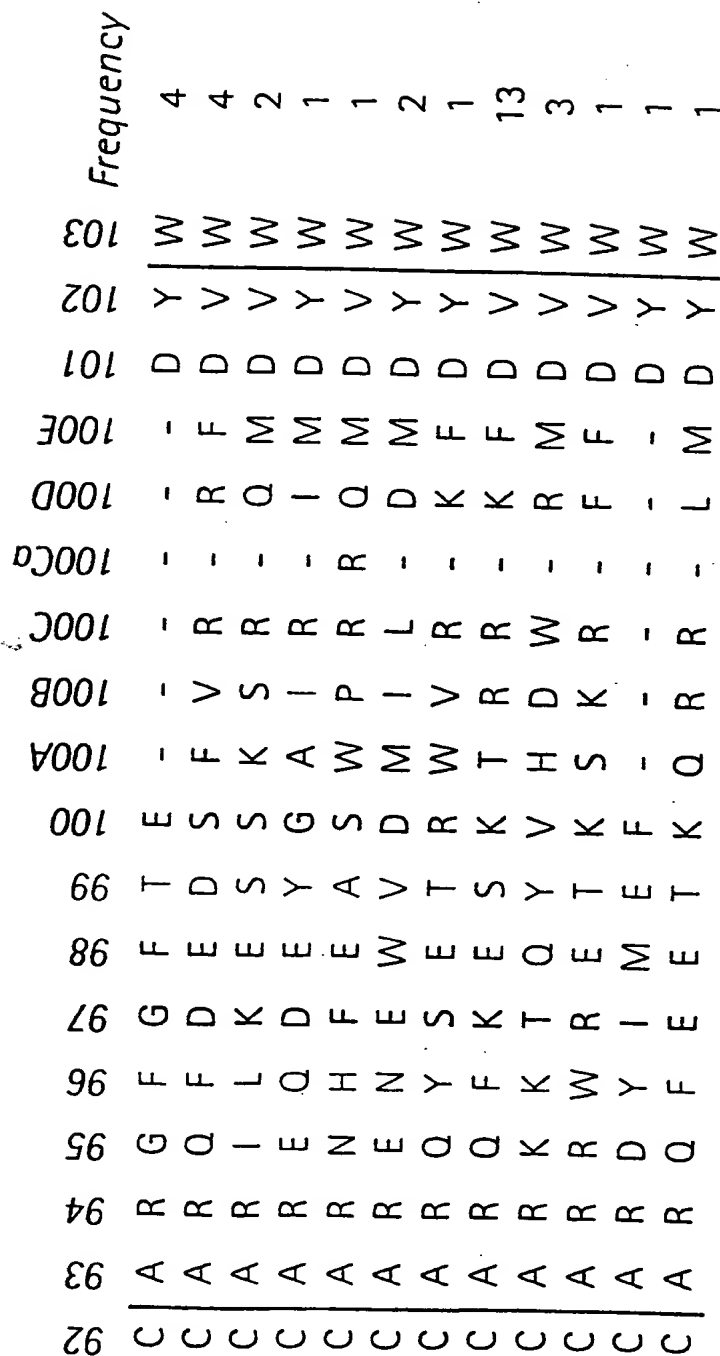
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Figure 22: Sequence analysis of lymphotoxin- $\beta$  binders

| Frequency |   |   |   |   |   |   |   |   |
|-----------|---|---|---|---|---|---|---|---|
| 103       | W | W | W | W | W | W | W | W |
| 102       | V | Y | Y | Y | Y | V | Y | Y |
| 101       | D | D | D | D | D | D | D | D |
| 100E      | F | M | F | M | M | F | M | F |
| 100D      | H | P | Q | W | V | S | W | W |
| 100C      | G | D | V | H | H | Q | E | Y |
| 100B      | K | Y | W | H | D | T | N | W |
| 100A      | I | S | Y | P | R | F | E | F |
| 100       | K | N | N | K | A | Q | T | I |
| 99        | S | F | D | L | Q | S | Q | L |
| 98        | R | D | L | Y | E | N | F | T |
| 97        | Y | R | D | A | I | H | H | P |
| 96        | R | W | A | Q | L | W | D | W |
| 95        | Q | M | L | R | S | V | D |   |
| 94        | R | R | R | R | R | R | R |   |
| 93        | A | A | A | A | A | A | A |   |
| 92        | C | C | C | C | C | C | C |   |

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**Figure 23: Sequence analysis of ESL-1 binders**

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Figure 24: Sequence analysis of BSA binders

| Frequency |             |
|-----------|-------------|
| 103       | W W W W W W |
| 102       | Y V V Y Y V |
| 101       | D D D D D D |
| 100E      | M F M M M F |
| 100D      | V R R Q Y F |
| 100C      | Y F V S W H |
| 100B      | D Y V W N T |
| 100A      | I N E S P L |
| 100       | A Y M L A P |
| 99        | Y M Q R W K |
| 98        | F Y E Y R F |
| 97        | G T F E S G |
| 96        | Q F F K P G |
| 95        | D V V E Y D |
| 94        | R R R R R R |
| 93        | A A A A A A |
| 92        | C C C C C C |

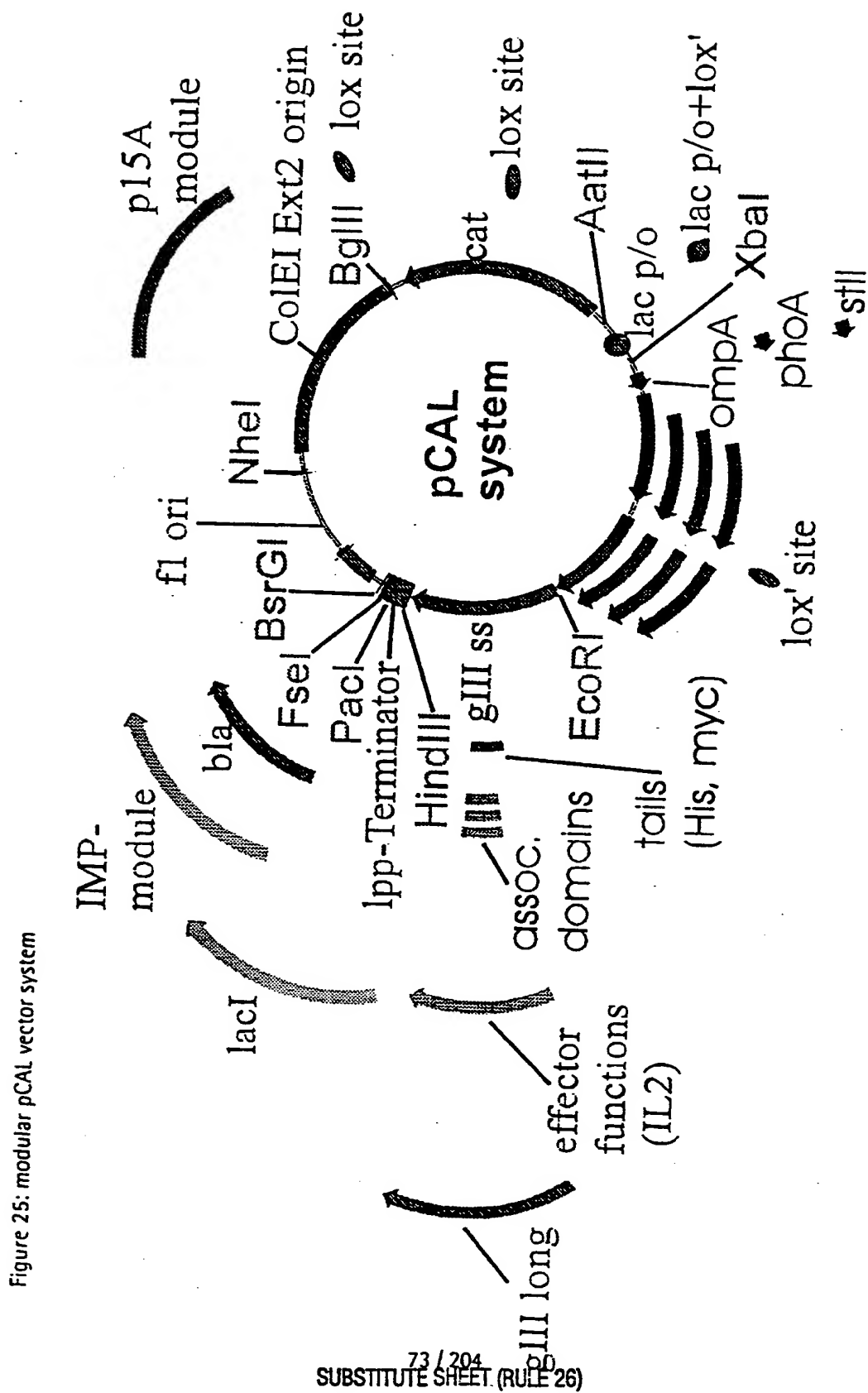


Figure 25a: List of unique restriction sites used in or suitable for HuCAL genes or pCAL vectors

| unique restriction site | Isoschizomers                     |
|-------------------------|-----------------------------------|
| AatII                   | /                                 |
| AflII                   | BfrI, BspTI, Bst98I               |
| AscI                    | /                                 |
| Asel                    | Vspl, AsnI, PshBI                 |
| BamHI                   | BstI                              |
| BbeI                    | EheI, KasI, NarI                  |
| BbsI                    | BpuAI, BpiI                       |
| BglII                   | /                                 |
| BlpI                    | Bpu1102I, CelII, BliI             |
| BsaBI                   | MamI, Bsh1365I, BsrBRI            |
| BsiWI                   | Pfi23II, SphI, SnuI               |
| BspEI                   | AccIII, BseAI, BsiMI, Kpn2I, MroI |
| BsrGI                   | Bsp1407I, SspBI                   |
| BssHII                  | Paul                              |
| BstEII                  | BstPI, Eco91I, EcoO65I            |
| BstXI                   | /                                 |
| Bsu36I                  | AocI, CvnI, Eco81I                |
| DraIII                  | /                                 |
| DsmAI                   |                                   |
| EagI                    | BstZI, EclXI, Eco52I, XmaIII      |
| Eco57I                  | /                                 |
| EcoO109I                | DraII                             |
| EcoRI                   | /                                 |
| EcoRV                   | Eco32I                            |
| FseI                    | /                                 |
| HindIII                 | /                                 |
| HpaI                    | /                                 |
| KpnI                    | Acc65I, Asp718I                   |
| MluI                    | /                                 |
| MscI                    | BalI, MluNI                       |

Figure 25a: List of unique restriction sites used in or suitable for HuCAL genes or pCAL vectors

| unique restriction site | Isoschizomers                      |
|-------------------------|------------------------------------|
| MunI                    | MfeI                               |
| NheI                    | /                                  |
| NsiI                    | Ppu10I, EcoT22I, Mph1103I          |
| NspV                    | Bsp119I, BstBI, Csp45I, LspI, SfuI |
| PacI                    | /                                  |
| PmeI                    | /                                  |
| PmlI                    | BbrPI, Eco72I, PmaCI               |
| Psp5II                  | PpuMI                              |
| PstI                    | /                                  |
| RsrII                   | (RsrI), CpoI, CspI                 |
| SanDI                   | /                                  |
| SapI                    | /                                  |
| SexAI                   | /                                  |
| SpeI                    | /                                  |
| SfiI                    | /                                  |
| SphI                    | BbuI, PaeI, NspI                   |
| StuI                    | AatI, Eco147I                      |
| StyI                    | Eco130I, EcoT14I                   |
| XbaI                    | BspLU11II                          |
| XhoI                    | PaeR7I                             |
| XmaI                    | AvaI, SmaI, Cfr9I, PspAI           |



Figure 26: list of pCAL vector modules

| No   | module/flanking restriction sites | functional element                                            | sites to be removed | sites to be inserted | template      | reference                                                                                                                           |
|------|-----------------------------------|---------------------------------------------------------------|---------------------|----------------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------|
| M1   | AatII-lacp/o-XbaI                 | lac promoter/operator                                         | 2x VspI (AseI)      | AatII                | vector pASK30 | Skerra et al. (1991) Bio/Technology 9, 273-278                                                                                      |
| M2   | BglII-lox-AatII                   | Cre/lox recombination site                                    | 2x VspI (AseI)      | lox, BglII           | (synthetic)   | Hoess et al. (1986) Nucleic Acids Res. 2287-2300                                                                                    |
| M3   | XbaI-lox'-SphI                    | Cre/lox' recombination site                                   | none                | lox', SphI           | (synthetic)   | see M2                                                                                                                              |
| M7-I | EcoRI-glllong-HindIII             | gllp of filamentous phage with N-terminal myctail/amber codon | SphI, BamHI         | none                 | vector pLG10  | Ge et al., (1994) Expressing antibodies in E. coli. In: Antibody engineering: A practical approach. IRL Press, New York, pp 229-266 |

Figure 26: list of pCAL vector modules

|         |                      |                                                                          |                            |                   |              |          |
|---------|----------------------|--------------------------------------------------------------------------|----------------------------|-------------------|--------------|----------|
| M7-II   | EcoRI-gIIIss-HindIII | truncated gIIIp of filamentous phage with N-terminal Gly-Ser linker      | SphI                       |                   | vector pIG10 | see M7-I |
| M7-III  | EcoRI-gIIIss-HindIII | truncated gIIIp of filamentous phage with N-terminal myctail/amber codon | SphI, BbsI                 |                   | vector pIG10 | see M7-I |
| M8      | SphI-lox-HindIII     | Cre/lox recombination site                                               | none                       | lox               | (synthetic)  | see M3   |
| M9-II   | HindIII-lpp-PacI     | lpp-terminator                                                           | none                       | PacI, FseI        | (synthetic)  | see M1   |
| M10-II  | PacI/FseI-bla-BsrGI  | beta-lactamase/bla (ampR)                                                | VspI, Eco57I, BssSI        | PacI, FseI, BsrGI | pASK30       | see M1   |
| M11-II  | BsrGI-f1 ori-NheI    | origin of single-stranded replication                                    | DrallI (BanII not removed) | BsrGI, NheI       | pASK30       | see M1   |
| M11-III | BsrGI-f1 ori-NheI    | origin of single-stranded replication                                    | DrallI, BanII              | BsrGI, NheI       | pASK30       | see M1   |

Figure 26: list of pCAL vector modules

|          |                      |                                                       |                            |                  |             |                                                                  |
|----------|----------------------|-------------------------------------------------------|----------------------------|------------------|-------------|------------------------------------------------------------------|
| M12      | NheI-p15A-BgIII      | origin of double-stranded replication                 | BssSI, VspI, NspV          | NheI, BgIII      | pACYC184    | Rose, R.E. (1988) Nucleic Acids Res. 16, 355                     |
| M13      | BgIII-lox-BgIII      | Cre/lox recombination site                            | none                       | BgIII, lox, XmnI | (synthetic) | see M3                                                           |
| M14-Ext2 | BgIII-ColEI-NheI     | origin of double-stranded replication                 | Eco57I (BssSI not removed) | BgIII, NheI      | pUC19       | Yanisch-Peron, C. (1985) Gene 33,103-119                         |
| M17      | AatII-cat-BgIII      | chloramphenicol-acetyltransferase/cat (camR)          | BspEI, MscI, StyI/NcoI     |                  | pACYC184    | Cardoso, M. & Schwarz, S. (1992) J. Appl. Bacteriol. 72, 289-293 |
| M19      | XbaI-phoA-EcoRI      | signal sequence of phosphatase A                      | (synthetic)                |                  | (synthetic) | see M1                                                           |
| M20      | XbaI-phoA-FLAG-EcoRI | signal sequence of phosphatase A + FLAG detection tag | (synthetic)                |                  | (synthetic) | Knappik, A & Plückthun, A. (1994) BioTechniques 17, 754-761      |

Figure 26: list of pCAL vector modules

|     |                       |                                            |                                                    |  |             |                                                                               |
|-----|-----------------------|--------------------------------------------|----------------------------------------------------|--|-------------|-------------------------------------------------------------------------------|
| M21 | XbaI-stII-SapI        | heat-stable enterotoxin II signal sequence | (synthetic)                                        |  | (synthetic) | Lee et al. (1983) Infect. Immunol. 264-268                                    |
| M41 | AflII-lacI-NheI       | lac-repressor                              | BstXI, MluI, BbsI, BanII, BstEII, HpaI, BbeI, VspI |  | pASK30      | see M1                                                                        |
| M42 | EcoRI-Histail-HindIII | poly-histidine tail                        | (synthetic)                                        |  | (synthetic) | Lindner et al., (1992) Methods: a companion to methods in enzymology 4, 41-56 |

Figure 27: functional map and sequence of MCS module

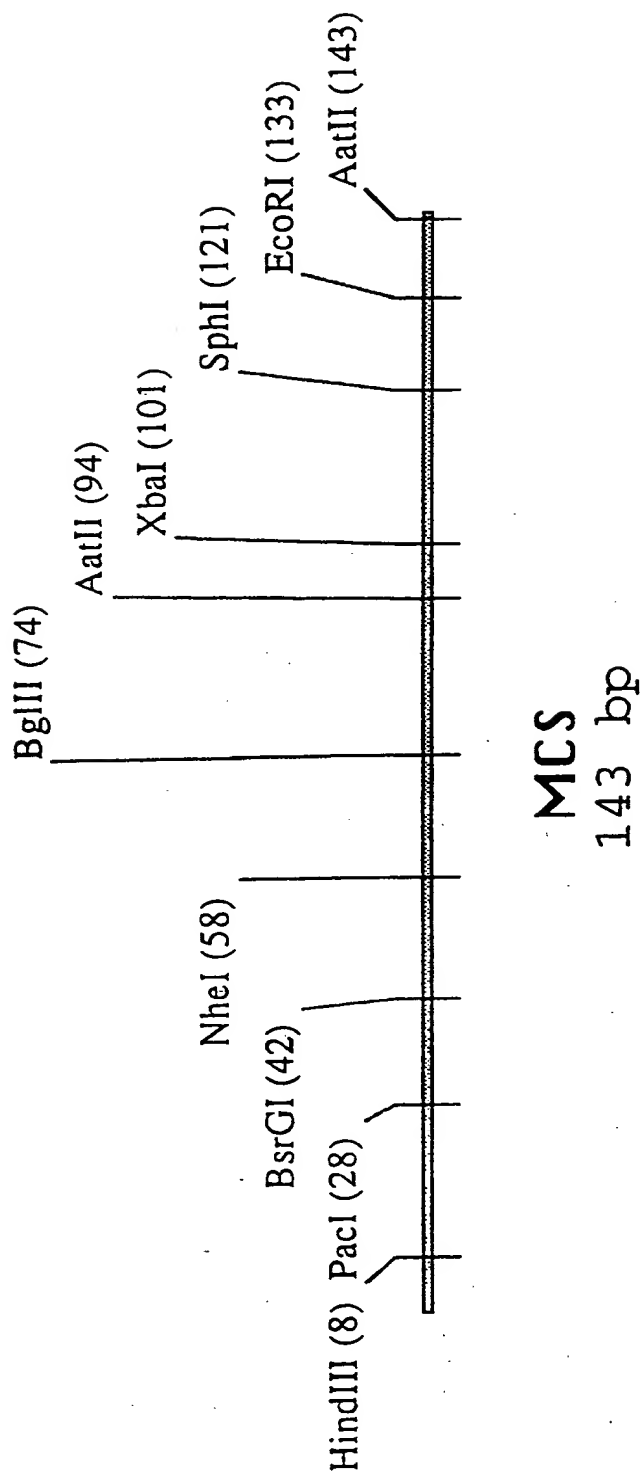


Figure 27: functional map and sequence of MCS module (continued)

|     | HindIII                                                                                                          | PacI  | BsrGI      |
|-----|------------------------------------------------------------------------------------------------------------------|-------|------------|
| 1   | ACATGTAAGC TTCCCCCCCC CCTTAATTAA CCCCCCCCCC TGTACACCCC<br>TGTACATTTCG AAGGGGGGGG GGAATTAATT GGGGGGGGG ACATGTGGGG |       |            |
| 51  | CCCCCGGCTA GCCCCCCCCC CCAGATCTCC CCCCCCCCCG CGTCCCCCCT<br>GGGGGGCGAT CGGGGGGGG GGTCTAGAGG GGGGGGGCT GCAGGGGGGA   | BglII | AatII XbaI |
| 101 | XbaI SphI EcoRI AatII                                                                                            |       |            |
|     | CTAGACCCC CCCCCGCATG CCCCCCCCCC CGAATTCGAC GTC<br>GATCTGGGG GGGGGCGTAC GGGGGGGGG GCTTAAGCTG CAG                  |       |            |

Figure 28: functional map and sequence of pMCS cloning vector

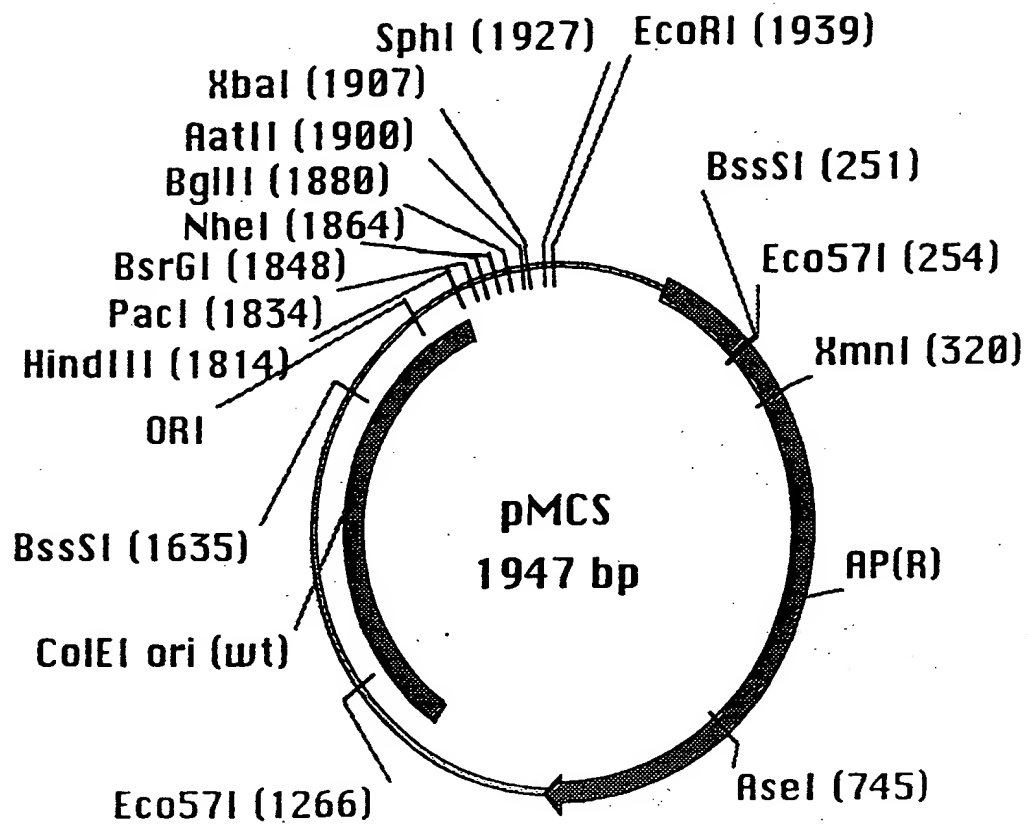


Figure 28: functional map and sequence of pMCS cloning vector (continued)

```

1  CAGGTGGCAC TTTTCGGGA AATGTGCGCG GAACCCCTAT TTGTTTATTT
   GTCCACCGTG AAAAGCCCTT TTACACGCGC CTGGGGGATA AACAAATAAA

51  TTCCTAAATAC ATTCAAATAT GTATCCGCTC ATGAGACAAAT AACCTGATA
   AAGATTATG TAAAGTTTATA CATAGGCGAG TACTCTGTTA TTGGGACTAT

101 AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTC
   TTACGGAAGTT ATTATAACTT TTTCCTTCTC ATACTCATAA GTTGTAAGG

151 GTGTCGCCCT TATCCCTTT TTTGCGGCAT TTTGCCCTTCC TGTTTTGTCT
   CACAGCGGA ATAAGGAAA AAACGCCGTA AAACGGAAGG ACAAAAACGA

                                     Eco57I
                                     ~~~~~

201 CACCAGAAA CGCTGGTGAA AGTAAAGAT GCTGAAGATC AGTTGGGTGC
   GTGGGTCTTT GCGACCACTT TCATTTTCTA CGACTTCTAG TCAACCCACG
                                     BssSI
                                     ~~~~~

251 ACGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA
   TGCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCCATTC TAGGAACCTCT
   BssSI
   ~~~~~

```



Figure 28: functional map and sequence of pMCS cloning vector (continued)

XmnI

~~~~~

|     |            |             |             |            |            |
|-----|------------|-------------|-------------|------------|------------|
| 301 | GTTTTCGCC  | CGAAGAACGT  | TTTCCAATGA  | TGAGCACTTT | TAAAGTTCTG |
|     | CAAAAGCGGG | GCTTCTTGCA  | AAAGGTTACT  | ACTCGTGAAA | ATTTCAGAC  |
| 351 | CTATGTGGCG | CGGTATTATC  | CCGTATTGAC  | GCCGGGCAAG | AGCAACTCGG |
|     | GATACACCGC | GCCATAATAG  | GGCATAAATG  | CGGCCCGTTC | TCGTTGAGCC |
| 401 | TCGCCGCATA | CACTATTCTC  | AGAATGACTT  | GGTTGAGTAC | TCACCAGTCA |
|     | AGCGGCGTAT | GTGATAAGAG  | TCTTACTGAA  | CCAACTCATG | AGTGGTCAGT |
| 451 | CAGAAAGCA  | TCTTACGGAT  | GGCATGACAG  | TAAGAGAATT | ATGCAGTGCT |
|     | GTCTTTTCGT | AGAAATGCCTA | CCGTACTGTC  | ATTCTCTTAA | TACGTCACGA |
| 501 | GCCATAACCA | TGAGTGATAA  | CAC TGCGGCC | AACTTACTTC | TGACAACGAT |
|     | CGGTATTGGT | ACTCACTATT  | GTGACGCCCG  | TTGAATGAAG | ACTGTTGCTA |
| 551 | CGGAGGACCG | AAGAGCTAA   | CCGCTTTTTC  | GCACAACATG | GGGGATCATG |
|     | GCCTCCTGGC | TTCCCTCGATT | GGCGAAAAAA  | CGTGTGTAC  | CCCCTAGTAC |
| 601 | TAACTCGCCT | TGATCGTTGG  | GAACCGGAGC  | TGAATGAAGC | CATACCAAAC |
|     | ATTGAGCGGA | ACTAGCAACC  | CTTGCCCTCG  | ACTTACTTCG | GTATGGTTTG |
| 651 | GACGAGCGTG | ACACCACGAT  | GCCTGTAGCA  | ATGGCAACAA | CGTTGCGCAA |

Figure 28: functional map and sequence of pMCS cloning vector (continued)

|      |             |            |             |             |             |
|------|-------------|------------|-------------|-------------|-------------|
|      | CTGCTCGCAC  | TGTGGTGCTA | CGGACATCGT  | TACCGTTGTT  | GCAACGCGTT  |
|      |             |            |             | AseI        |             |
|      |             |            |             | ~~~~~       |             |
| 701  | ACTATTAACT  | GGCGAACTAC | TTACTCTAGC  | TTCCCGGGCAA | CAATTAAATAG |
|      | TGATAAATTGA | CCGCTTGATG | AATGAGATCG  | AAGGGCCCGTT | GTTAATTATC  |
| 751  | ACTGGATGGA  | GGCGGATAAA | GTTGCAGGAC  | CAC TTCTGCG | CTCGGCCCTT  |
|      | TGACCTACCT  | CCGCCATATT | CAACGTCCCTG | GTGAAGACGC  | GAGCCGGGAA  |
| 801  | CCGGCTGGCT  | GGTTTATTGC | TGATAAATCT  | GGAGCCGGTG  | AGCGTGGGTC  |
|      | GGCCGACCGA  | CCAAATAACG | ACTATTTAGA  | CCTCGGCCAC  | TCGCACCCAG  |
| 851  | TCGCGGTATC  | ATTGCAGCAC | TGGGGCCAGA  | TGGTAAGCCC  | TCCC GTATCG |
|      | AGCGCCATAG  | TAACGTCGTG | ACCCCGGTCT  | ACCATTCGGG  | AGGCGATAGC  |
| 901  | TAGTTATCTA  | CACGACGGGG | AGTCAGGCAA  | CTATGGATGA  | ACGAAATAGA  |
|      | ATCAATAGAT  | GTGCTGCCCC | TCAGTCCGTT  | GATACCTACT  | TGCTTTATCT  |
| 951  | CAGATCGCTG  | AGATAGGTGC | CTCACTGATT  | AAGCATTTGGT | AACGTGCAGA  |
|      | GTCTAGCGAC  | TCTATCCACG | GAGTGACTAA  | TTCGTAACCA  | TTGACAGTCT  |
| 1001 | CCAAGTTTAC  | TCATATATAC | TTTAGATTGA  | TTTAAAACTT  | CATTTTAAAT  |
|      | GGTTCAAATG  | AGTATATATG | AAATCTAACT  | AAATTTTGAA  | GTAAAAATTA  |

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Figure 28: functional map and sequence of pMCS cloning vector (continued)

```

1051  TTAAGAGGAT CTAGGTGAAG ATCCTTTTGG ATAATCTCAT GACCAAAATC
      AATTTCCCTA GATCCACTTC TAGGAAAAC  TATTAGAGTA CTGGTTTTAG

1101  CCTTAACGTG AGTTTTCGTT CCACTGAGCG TCAGACCCCG TAGAAAAGAT
      GGAATTGCAC TCAAAAGCAA GTGACTCGC AGTCTGGGC ATCTTTTCTA

1151  CAAAGGATCT TCTTGAGATC CTTTTTCTTCT GCGCGTAATC TGCTGCTTGC
      GTTTCCTAGA AGAACTCTAG GAAAAAAGA CGGCATTAG ACGACGAACG

1201  AAACAAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC GGATCAAGAG
      TTTGTTTTTT TGGTGGCGAT GTCGCCACC AAACAAACGG CCTAGTTCTC

1251  CTACCAACTC TTTTCCGAA GGTAAC TGC TGCAGATACC CGCAGATACC
      GATGGTTGAG AAAAAGGCTT CCATTGACCG AAGTCGTCTC GCGTCTATGG
                               Eco57I
                               ~~~~~

1301  AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC TTCAAGAACT
      TTTATGACAG GAAGATCACA TCGGCATCAA TCCGGTGGTG AAGTCTTGA

1351  CTGTAGCACC GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT
      GACATCGTGG CGGATGTATG GAGCGAGACG ATTAGGACAA TGGTCACCGA

```

Figure 28: functional map and sequence of pMCS cloning vector (continued)

|      |             |             |             |             |             |
|------|-------------|-------------|-------------|-------------|-------------|
| 1401 | GCTGCCAGTG  | GGATAAGTC   | GTGTCTTACC  | GGGTTGGACT  | CAAGACGATA  |
|      | CGACGGTCAC  | CGCTATTTCAG | CACAGAATGG  | CCCAACCTGA  | GTTCTGCTAT  |
| 1451 | GTTACCGGAT  | AAGGCGCAGC  | GGTCGGGCTG  | AACGGGGGGT  | TCGTGACACAC |
|      | CAATGGCCCTA | TTCCGCGTCG  | CCAGCCCGAC  | TTGCCCCCCCA | AGCACGTGTG  |
| 1501 | AGCCCAGCTT  | GGAGCGAAGC  | ACCTACACCG  | AACTGAGATA  | CCTACAGCGT  |
|      | TCGGGTCGAA  | CCTCGCTTGC  | TGGATGTGGC  | TTGACTCTAT  | GGATGTGCA   |
| 1551 | GAGCTATGAG  | AAAGCGCCAC  | GCTTCCCCGAA | GGGAGAAAGG  | CGGACAGGTA  |
|      | CTCGATACTC  | TTTCGCGGTG  | CGAAGGGCTT  | CCCTCTTTCC  | GCCTGTCCAT  |
| 1601 | TCCGGTAAGC  | GGCAGGGTCG  | GAACAGGAGA  | GCGCACGAGG  | GAGCTTCCAG  |
|      | AGGCCATTTCG | CCGTCCCAGC  | CTTGTCCTCT  | CGCGTGCTCC  | CTCGAAGGTC  |
|      |             |             |             | BssSI       |             |
|      |             |             |             | ~~~~~       |             |
| 1651 | GGGAAACGC   | CTGGTATCTT  | TATAGTCCTG  | TCGGGTTTCG  | CCACCTCTGA  |
|      | CCCCTTTGCG  | GACCATAGAA  | ATATCAGGAC  | AGCCCAAAGC  | GGTGGAGACT  |
| 1701 | CTTGAGCGTC  | GATTTTGTG   | ATGCTCGTCA  | GGGGGGCGGA  | GCCTATGGAA  |
|      | GAACTCGCAG  | CTAAAAACAC  | TACGAGCAGT  | CCCCCCGCCT  | CGGATACCTT  |
| 1751 | AAACGCCAGC  | AACGGGCCT   | TTTTACGGTT  | CCTGGCCTTT  | TGCTGGCCCTT |

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Figure 28: functional map and sequence of pMCS cloning vector (continued)

```

TTTGCGGTCTG TTGCGCCCGGA AAAATGCCAA GGACCGGAAA ACGACCGGAA

      HindIII          PacI          BsrGI
      ~~~~~          ~~~~~          ~~~~~
1801 TTGCTCACAT GTAAGCTTCC CCCCCCCTT AATTAACCC CCCCCCTGTA
      AACGAGTGTA CATTGGAAG GGGGGGGAA TTAATTGGG GGGGGGACAT

      BsrGI          NheI          BglII          AatII
      ~~~~~          ~~~~~          ~~~~~          ~~~~~
1851 CACCCCCCCC CCGTAGCCG CCCCCCCCAG ATCTCCCCC CCCCAGCGTC
      GTGGGGGGGG GCGATCGGG GGGGGGGGTC TAGAGGGGG GGGGCTGCAG

      XbaI          SphI          EcoRI
      ~~~~~          ~~~~~          ~~~~~
1901 CCCCTCTAG ACCCCCCCCC CGCATGCCCC CCCCCCGAA TTCACGT
      GGGGAGATC TGGGGGGGGG GCGTACGGG GGGGGGCTT AAGTGCA

```

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Figure 29: functional map and sequence of pCAL module M1

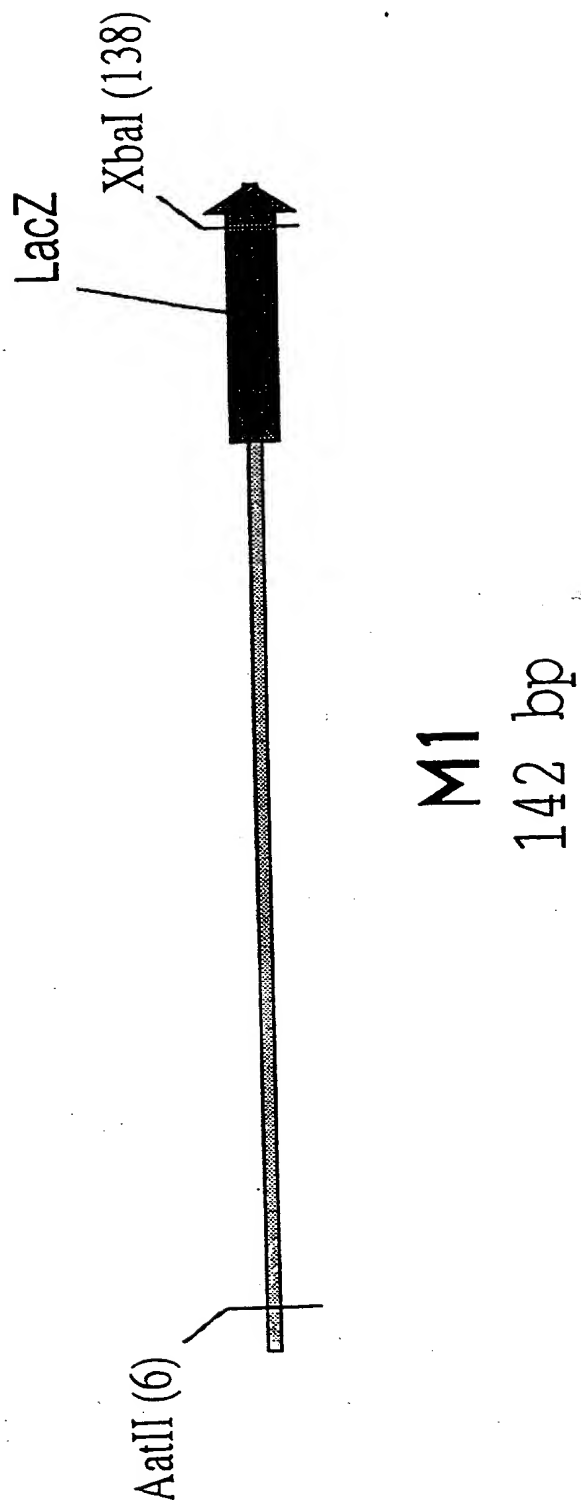


Figure 29: functional map and sequence of pCAL module M1

AatII  
~~~~~

1 GACGTCCTAA TGTGAGTTAG CTCACTCATT AGGCACCCCA GGCTTTACAC  
CTGCAGAAAT ACACCTCAATC GAGTGAGTAA TCCGTGGGGT CCGAAATGTG

51 TTTATGCTTC CGGCTCGTAT GTTGTGTGGA ATTGTGAGCG GATAACAATT  
AAATACGAAG GCCGAGCATA CAACACACCT TAACACTCGC CTATTGTTAA

XbaI  
~~~~~

101 TCACACAGGA AACAGCTATG ACCATGATTA CGAATTCTA GA  
AGTGTGTCCT TTGTCGATAC TGGTACTAAT GCTTAAAGAT CT

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Figure 30: functional map and sequence of pCAL module M7-II

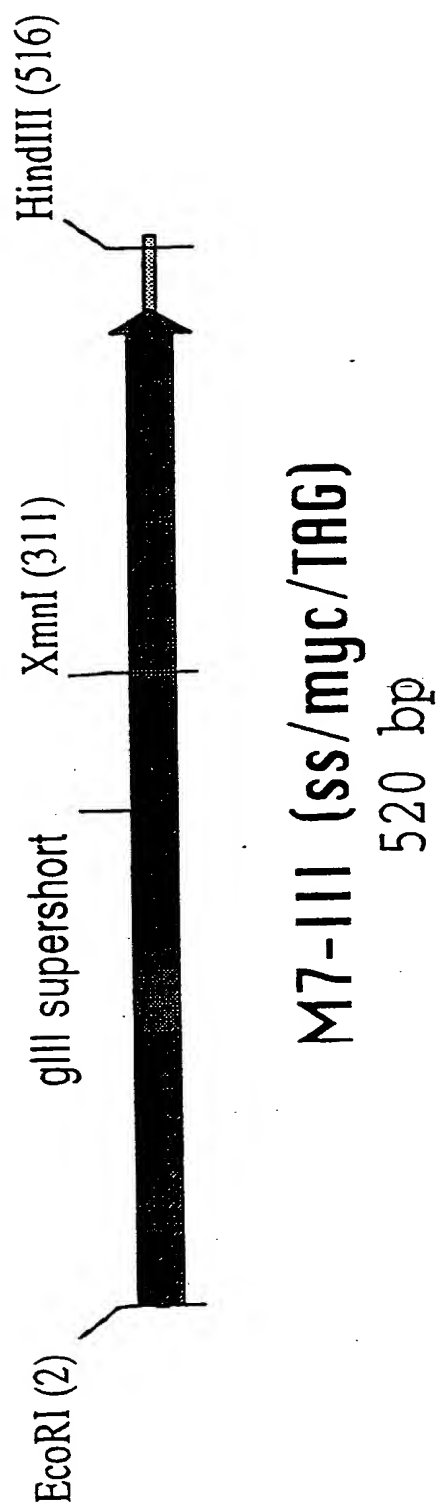




Figure 30: functional map and sequence of pCAL module M7-II (continued)

EcoRI  
 ~~~~~  
 1 GAATTCGAGC AGAAGCTGAT CTCGTAGGAG GATCTGTAGG GTGGTGGCTC  
 CTTAAGCTCG TCTTCGACTA GAGACTCCTC CTAGACATCC CACCACCGAG  
 51 TGGTTCGGT GATTTTGATT ATGAAAAGAT GGCAACGCT AATAAGGGG  
 ACCAAGGCCA CTAAAACTAA TACTTTTCTA CCGTTTGCGA TTATTCCCCC  
 101 CTATGACCGA AAATGCCGAT GAAACGCGC TACAGTCTGA CGCTAAAGGC  
 GATACTGGCT TTTACGGCTA CTTTGGCGG ATGTCAGACT GCGATTTCGG  
 151 AAACCTTGATT CTGTCGCTAC TGATTACGGT GCTGCTATCG ATGGTTTCAT  
 TTTGAACTAA GACAGCGATG ACTAATGCCA CGACGATAGC TACCAAAGTA  
 201 TGGTGACGTT TCCGGCCTTG CTAATGGTAA TGGTGCTACT GGTGATTTTG  
 ACCACTGCAA AGGCCGGAAC GATTACCATT ACCACGATGA CCACTAAAC  
 251 CTGGCTCTAA TTCCCAAATG GCTCAAGTCG GTGACGGTGA TAATTCACCT  
 GACCGAGATT AAGGGTTTAC CGAGTTCAGC CACTGCCACT ATTAAGTGGA  
 XmnI  
 ~~~~~  
 301 TTAATGAATA ATTTCCGTCA ATATTACCT TCCCTCCCTC AATCGGTGA  
 AATTACTTAT TAAAGGCAGT TATAAATGGA AGGAGGGAG TTAGCCAACT

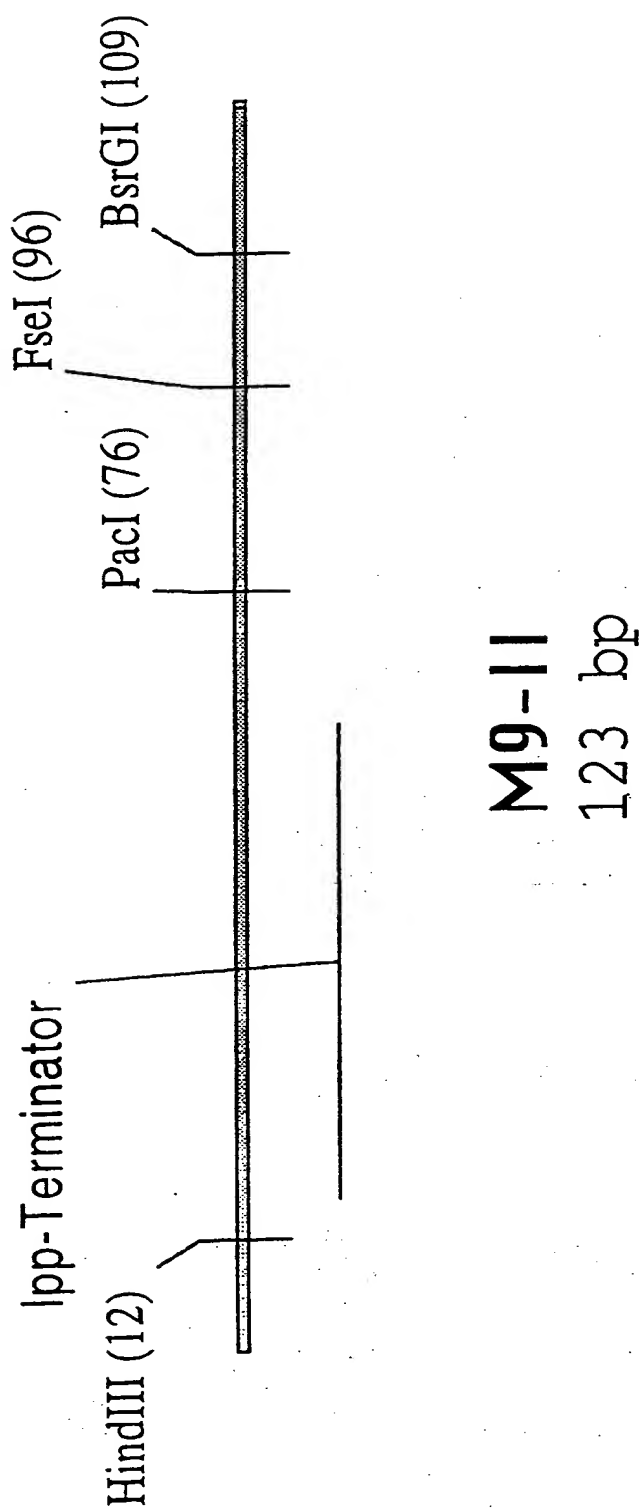
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Figure 30: functional map and sequence of pCAL module M7-II (continued)

|     |            |             |            |            |            |
|-----|------------|-------------|------------|------------|------------|
| 351 | ATGTCGCCCT | TTTGTCCTTG  | GCGCTGGTAA | ACCATATGAA | TTTTCTATTG |
|     | TACAGCGGGA | AAACAGAAAC  | CGCGACCAT  | TGGTATACTT | AAAAGATAAC |
| 401 | ATTGTGACAA | AATAAACTTA  | TTCCGTGGTG | TCCTTGCGGT | TCCTTTATAT |
|     | TAAACACTGT | TTATTGGAAT  | AAGGCACCA  | AGAAACGCAA | AGAAATATA  |
| 451 | GTTGCCACCT | TTATGTATGT  | ATTTTCTACG | TTTGCTAACA | TACTGCGTAA |
|     | CAACGGTGGA | AATACATACA  | TAAAGATGC  | AAACGATTGT | ATGACGCATT |
| 501 | TAAGGAGTCT | TGATAAGCCT  |            |            |            |
|     | ATTCCTCAGA | ACTATTTCGAA |            |            |            |

HindIII  
~~~~~

Figure 31: functional map and sequence of pCAL module M9-II



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Figure 31: functional map and sequence of pCAL module M9-II (continued)

HindIII  
 ~~~~~  
 1 GGGGGGGGGG AAGCTTGACC TGTGAAGTGA AAAATGGCGC AGATTGTGCG  
 CCCCCCCCCC TTCGAACTGG ACACTTCACT TTTTACCGCG TCTAACACGC

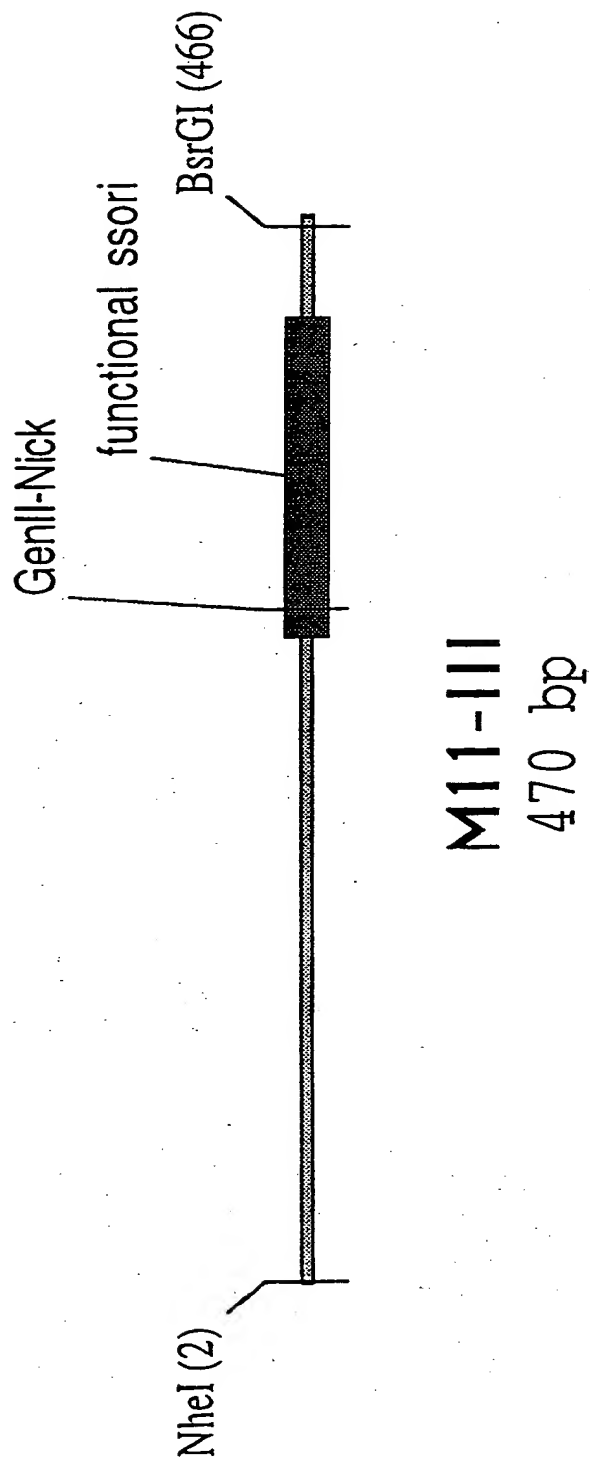
PacI  
 ~~~~~  
 51 ACATTTTTF TGTCTGCCGT TTAATTAAAG GGGGGGGGGG GCCGGCCTGG  
 TGTAATAAAA ACAGACGGCA AATTAAATTC CCCCCCCCCC CGCCCGGACC

FseI  
 ~~~~~

BsrGI  
 ~~~~~  
 101 GGGGGGGTGT ACAGGGGGG GGG  
 CCCCCCACA TGTCCCCCCC CCC

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Figure 32: functional map and sequence of pCAL module M11-III



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Figure 32: functional map and sequence of pCAL module M11-III (continued)

NheI  
~~~~~

|     |             |             |            |             |             |
|-----|-------------|-------------|------------|-------------|-------------|
| 1   | GCTAGCACGC  | GCCCTGTAGC  | GCGGCATTAA | GCGCGGCGGG  | TGTGGTGGTT  |
|     | CGATCGTGCG  | CGGACATCG   | CCGCGTAATT | CGCGCCGCC   | ACACCACCAA  |
| 51  | ACGCGCAGCG  | TGACCGCTAC  | ACTTGCCAGC | GCCCTAGCGC  | CCGCTCCTTT  |
|     | TGCGCGTCGC  | ACTGGCGATG  | TGAACGGTCG | CGGATCGCG   | GGCGAGGAAA  |
| 101 | CGCTTTCTTC  | CCTTCCTTTC  | TCGCCACGTT | CGCCGGCTTT  | CCCCGTCAAG  |
|     | GCGAAAGAAAG | GGAAGGAAAG  | AGCGGTGCAA | GCGGCCGAAA  | GGGCAGTTC   |
| 151 | CTCTAAATCG  | GGGCATCCCT  | TTAGGGTTCC | GATTAGTGC   | TTACGGGCAC  |
|     | GAGATTTAGC  | CCCGTAGGGA  | AATCCCAAGG | CTAAATCACG  | AAATGCCCGTG |
| 201 | CTCGACCCCA  | AAAACTTGA   | TTAGGGTGAT | GGTTCCTCGTA | GTGGGCCATC  |
|     | GAGCTGGGGT  | TTTTTTGAACT | AATCCCACTA | CCAAGAGCAT  | CACCCGGTAG  |
| 251 | GCCCTGATAG  | ACGGTTTTC   | GCCCTTTGAC | GTGAGAGTCC  | ACGTTCTTTA  |
|     | CGGGACTATC  | TGCCAAAAG   | CGGAAACTG  | CAACCTCAGG  | TGCAAGAAAT  |
| 301 | ATAGTGGACT  | CTTGTTCCAA  | ACTGGAACAA | CACCTCAACCC | TATCTCGGTC  |
|     | TATCACCTGA  | GAACAAGGTT  | TGACCTTGTT | GTGAGTTGGG  | ATAGAGCCAG  |
| 351 | TATTCTTTTG  | ATTTATAAGG  | GATTTGCCCG | ATTTCCGGCCT | ATTGGTTAAA  |

Figure 32: functional map and sequence of pCAL module M11-III (continued)

ATAAGAAAAC TAAATATTCC CTAAAACGGC TAAAGCCGGA TAACCAATT  
401 AAATGAGCTG ATTTAACAAA AATTTAACGC GAATTTTAAAC AAAATATTAA  
TTTACTCGAC TAAATTGTTT TTAAATTGCG CTTAAAATTG TTTTATAAATT

BsrGI

~~~~~

451 CGTTTACAAT TTCATGTACA  
GCAAAATGTTA AAGTACATGT

Figure 33: functional map and sequence of pCAL module M14-Ext2

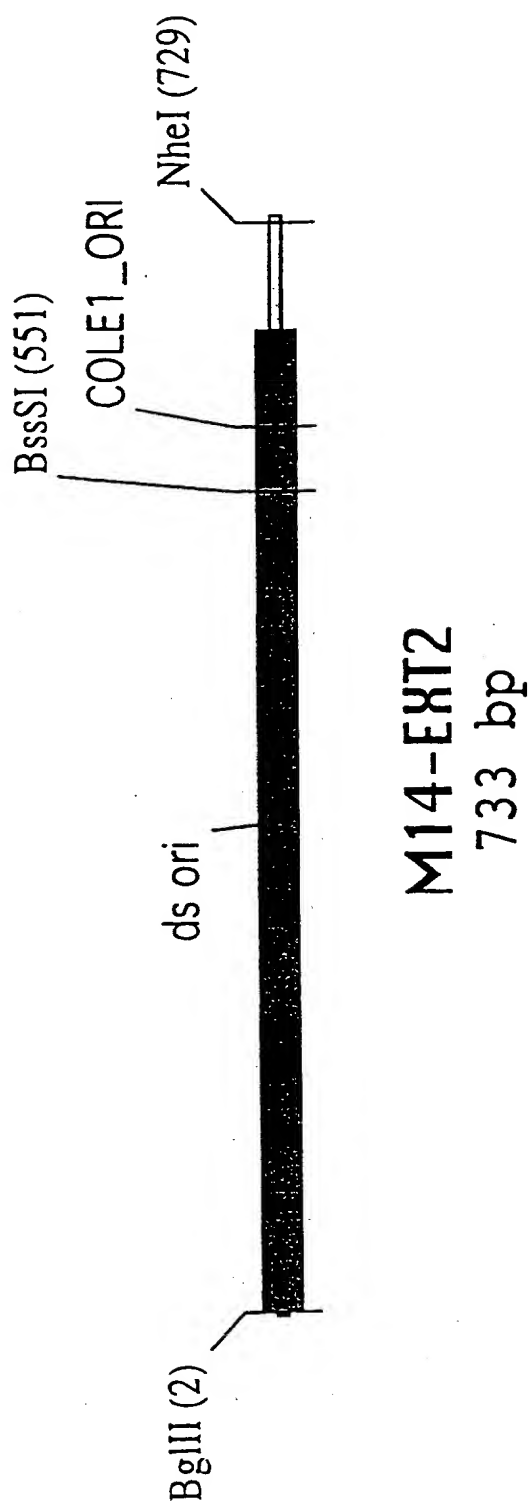




Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

## Bg1II

~~~~~

1 AGATCTGACC AAAATCCCTT AACGTGAGTT TTCGTTCAC TGAGCGTCAG  
TCTAGACTGG TTTTAGGAA TTGCACTCAA AAGCAAGTG ACTCGCAGTC

51 ACCCCGTAGA AAAGATCAAA GGATCTTCTT GAGATCCCTT TTTTCTGCGC  
TGGGGCATCT TTTCTAGTTT CCTAGAAGAA CTCTAGGAAA AAAAGACGCG

101 GTAATCTGCT GCTTGCAAAC AAAAAACCA CCGCTACCAG CGGTGGTTTG  
CATTAGACGA CGAACGTTG TTTTTTTGGT GCGGATGGTC GCCACCAAC

151 TTTGCCGGAT CAAGAGCTAC CAACTCTTTT TCCGAAGGTA ACTGGCTACA  
AAACGGCCTA GTTCTCGATG GTTGAGAAA AGGCTTCCAT TGACCGATGT

201 GCAGAGCGCA GATACCAAAT ACTGTTCTTC TAGTGTAGCC GTAGTTAGGC  
CGTCTCGCGT CTATGGTTA TGACAAGAAG ATCACATCGG CATCAATCCG

251 CACCACTTCA AGAACTCTGT AGCACCGCCT ACATACCCTCG CTCTGCTAAT  
GTGGTGAAGT TCTTGAGACA TCGTGGCGGA TGTATGGAGC GAGACGATTA

301 CCTGTTACCA GTGGCTGCTG CCAGTGGCGA TAAGTCGTGT CTTACCGGGT  
GGACAATGGT CACCGACGAC GGTACCGCT ATTCAGCACA GAATGGCCCCA

351 TGGACTCAAG ACGATAGTTA CCGGATAAG CGCAGCGGTC GGGCTGAACG

Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

```

ACCTGAGTTC TGCTATCAAT GGCTATTCC GCGTCGCCAG CCCGACTTGC
401 GGGGGTTTCGT GCACACAGCC CAGCTTGGAG CGAACGACCT ACACCGAACT
CCCCCAAGCA CGTGTGTCGG GTCGAACCTC GCTTGCTGGA TGTGGCTTGA
451 GAGATACCTA CAGCGTGAGC TATGAGAAAG CGCCACGCTT CCCGAAGGGA
CTCTATGGAT GTCGCACTCG ATACTCTTTC GCGGTGCGAA GGGCTTCCCT
501 GAAAGGCGGA CAGGTATCCG GTAAGCGGCA GGGTCGGAAC AGGAGAGCGC
CTTCCCGCCT GTCCATAGGC CATTCGCCGT CCCAGCCTTG TCCTCTCGCG
BssSI
551 ACGAGGGAGC TTCCAGGGGG AAACGCCCTGG TATCTTTATA GTCCCTGTCCG
TGCTCCCTCG AAGTCCCCC TTTGCGGACC ATAGAAATAT CAGGACAGCC
BssSI
~~~~~
601 GTTTCGCCAC CTCGACTTG AGCGTCGATT TTTGTGATGC TCGTCAGGGG
CAAAGCGGTG GAGACTGAAC TCGCAGCTAA AACACTACG AGCAGTCCCC
651 GCGGGAGCCT ATGGAAAAC GCCAGCAACG CGGCCTTTTC ACGGTTCCCTG
CCGCCTCGGA TACCTTTTTC CGGTCGTTGC GCCGGAAAAA TGCCAAGGAC

```

Figure 33: Functional map and sequence of pCAL module M14-Ext2 (continued)

NheI  
~~~~~

701 | GCCTTTTGCT GGCCTTTTGC TCACATGGCT AGC  
CGGAAACGA CCGGAAACG AGGTACCGA TCG

Figure 34: functional map and sequence of pCAL module M17

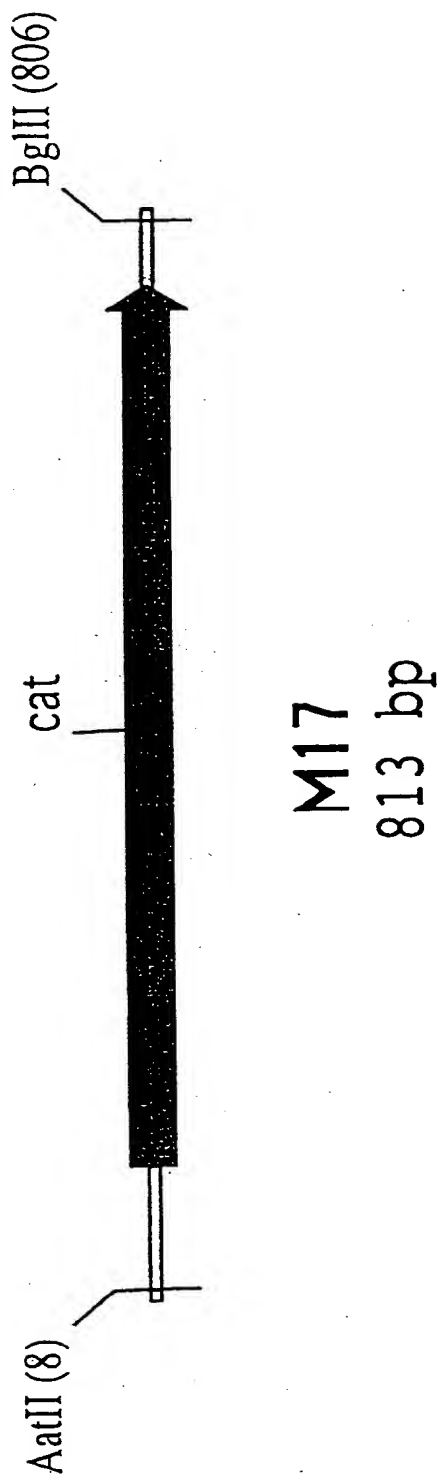


Figure 34: functional map and sequence of pCAL module M17. (continued)

## AatII

~~~~~

```

1  GGGACGTCGG GTGAGGTTCC AACTTTCACC ATAATGAAAT AAGATCACTA
   CCTGCGAGCC CACTCCAAGG TTGAAAGTGG TATTAATTTA TTCTAGTGAT

51  CCGGGCGTAT TTTTGTAGTT ATCGAGATT T CAGGAGCTA AGGAAGCTAA
   GGGCCGCATA AAAAAGCTCAA TAGCTCTAAA AGTCCCTCGAT TCCTTCGATT

101 AATGGAGAAA AAAATCACTG GATATACCAC CGTTGATATA TCCAATGGC
   TTACCTCTTT TTTTAGTGAC CTATATGGTG GCAACTATAT AGGGTTACCG

151 ATCGTAAAGA ACATTTTGAG GCATTTTCAGT CAGTTGCTCA ATGTACCTAT
   TAGCATTTCT TGTAAGAACTC CGTAAAGTCA GTCACGAGT TACATGGATA

201 AACCAGACCG TTCAGCTGGA TATTACGGCC TTTTAAAGA CCGTAAAGAA
   TTGGTCTGGC AAGTCGACCT ATAATGCCCGG AAAAATTTCT GGCATTTCTT

251 AAATAAGCAC AAGTTTATC CGGCCTTTAT TCACATTTCT GCCCGCCTGA
   TTTATTCGTG TTCAAAATAG GCCGGAATA AGTGTAAGAA CCGCGGACT

301 TGAATGCTCA CCCGGAGTTC CGTATGGCAA TGAAAGACGG TGAGCTGGTG
   ACTACGAGT GGGCCTCAAG GCATACCGTT ACTTTCTGCC ACTCGACCAC

351 ATATGGGATA GTGTTCACCC TTGTTACACC GTTTTCCATG AGCAAACCTGA

```

Figure 34: functional map and sequence of pCAL module M17 (continued)

|     |             |            |            |             |             |
|-----|-------------|------------|------------|-------------|-------------|
|     | TATACCCCTAT | CACAAGTGGG | AACAATGTGG | CAAAAGGTAC  | TCGTTTGACT  |
| 401 | AACGTTTTC   | TCGCTCTGGA | GTGAATACCA | CGACGATTTC  | CGGCAGTTTC  |
|     | TTGCAAAAGT  | AGCGAGACCT | CACTTATGGT | GCTGCTAAAG  | GCCGTCAAAG  |
| 451 | TACACATATA  | TTCGCAAGAT | GTGGCGTGTT | ACGGTGAAAA  | CCTGGCCCTAT |
|     | ATGTGTATAT  | AAGCGTTCTA | CACCGCACAA | TGCCACTTTT  | GGACCGGATA  |
| 501 | TTCCCTAAAG  | GGTTTATTGA | GAATATGTTT | TTCGTCTCAG  | CCAATCCCTG  |
|     | AAGGATTTC   | CCAAATAACT | CTTATACAAA | AAGCAGAGTC  | GGTAGGGAC   |
| 551 | GGTGAGTTC   | ACCAGTTTTC | ATTTAACGT  | AGCCAATATG  | GACAACCTCT  |
|     | CCACTCAAAG  | TGGTCAAAAC | TAAATTTGCA | TCGGTTATAC  | CTGTTGAAGA  |
| 601 | TCGCCCCCGT  | TTTCACTATG | GGCAAATATT | ATACGCAAGG  | CGACAAGGTG  |
|     | AGCGGGGGCA  | AAAGTGATAC | CCGTTTATAA | TATGCGTTCC  | GCTGTTCCAC  |
| 651 | CTGATGCCGC  | TGGCGATTCA | GGTTCATCAT | GCCGTTTGTG  | ATGGCTTCCA  |
|     | GACTACGGCG  | ACCGCTAAGT | CCAAGTAGTA | CGGCAAAACAC | TACCGAAGGT  |
| 701 | TGTCGGCAGA  | ATGCTTAATG | AATTACAACA | GTACTGCGAT  | GAGTGGCAGG  |
|     | ACAGCCGTCT  | TACGAATTAC | TTAATGTTGT | CATGACGCTA  | CTCACCCGTCC |
| 751 | GCGGGGCGTA  | ATTTTTTTAA | GGCAGTTATT | GGGTGCCCTT  | AAACGCCCTGG |

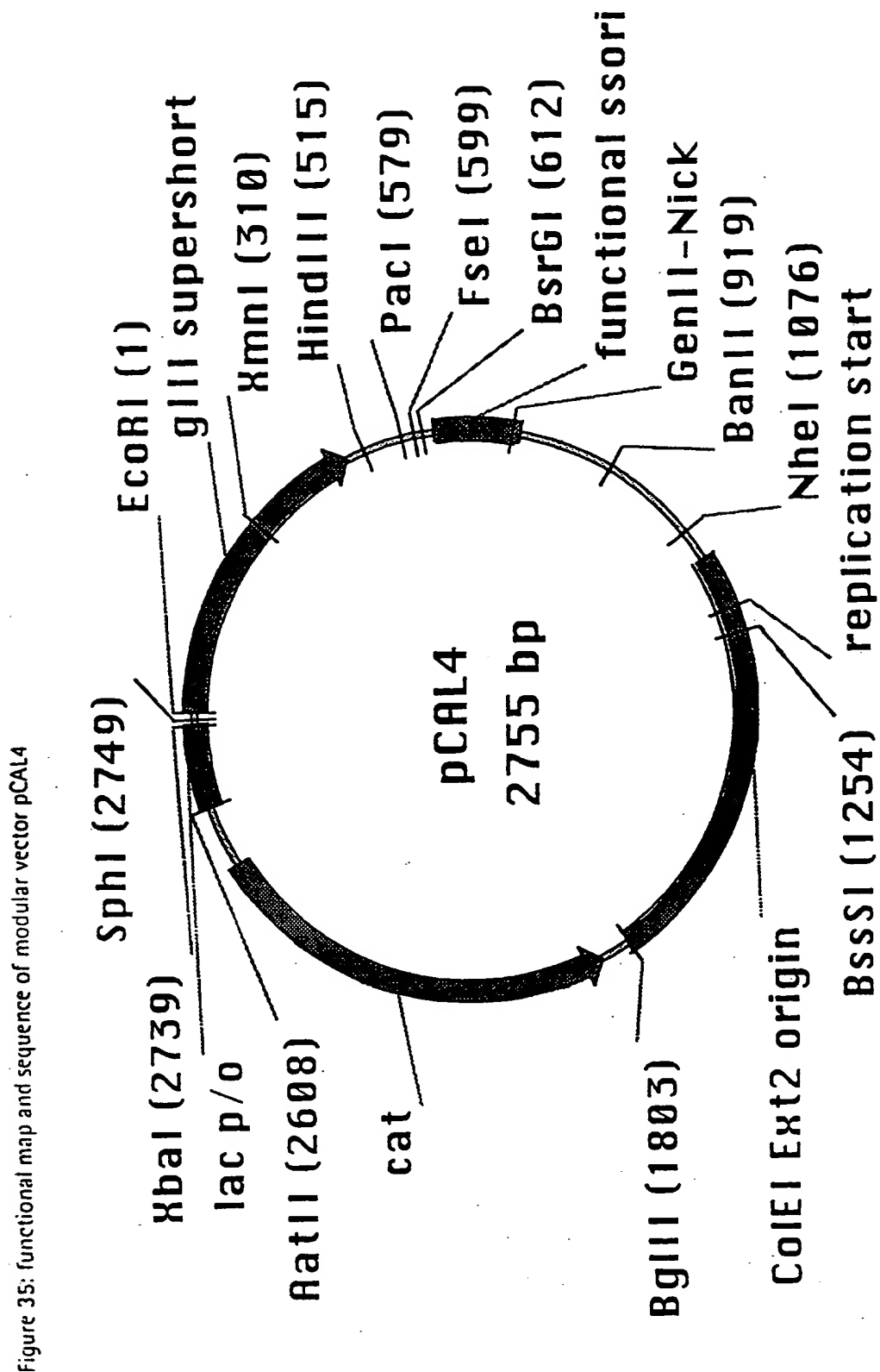
Figure 34: functional map and sequence of pCAL module M17 (continued)

CGCCCCGCAT TAAAAAATT CCGTCAATAA CCCACGGGAA TTTGCGGACC

BglII

~~~~~

801 TGCTAGATCT TCC  
ACGATCTAGA AGG



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Figure 35: functional map and sequence of modular vector pCAL4 (continued)

| EcoRI |   |
|-------|---|
| ~~~~~ |   |
| 1     | AATTCGAGCA GAAGCTGATC TCTGAGGAGG ATCTGTAGGG TGGTGGCTCT<br>TTAAGCTCGT CTTCGACTAG AGACTCCTCC TAGACATCCC ACCACCGAGA  |
| 51    | GGTCCGGTG ATTTTGATTA TGAAAGATG GCAAACGCTA ATAAGGGGC<br>CCAAGGCCAC TAAACTAAT ACTTTTCTAC CGTTGCGAT TATTCCTCCG       |
| 101   | TATGACCGAA AATGCCGATG AAAACGCGCT ACAGTCTGAC GCTAAAGGCA<br>ATACTGGCTT TTACGGCTAC TTTTGCGCGA TGTGAGACTG CGATTTCCTG  |
| 151   | AACTTGATTC TGTCGCTACT GATTACGGTG CTGCTATCGA TGGTTTCATT<br>TTGAACCTAAG ACAGCGATGA CTAATGCCAC GACGATAGCT ACCAAAGTAA |
| 201   | GGTGACGTTT CCGGCCCTGC TAATGGTAAT GGTGCTACTG GTGATTTTGC<br>CCACTGCCAA GGCCGGAACG ATTACCATTA CCACGATGAC CACTAAAACG  |
| 251   | TGGCTCTAAT TCCCAAATGG CTCAAGTCGG TGACGGTGAT AATTCACCTT<br>ACCGAGATTA AGGGTTTACC GAGTTCAGCC ACTGCCACTA TTAAGTGGAA  |
| XmnI  |   |
| ~~~~~ |   |
| 301   | TAATGAATAA TTTCGGTCAA TATTACCTT CCTCCCTCA ATCGGTGAA<br>ATTACTTATT AAAGGCAGTT ATAAATGGAA GGGAGGGAGT TAGCCAACTT     |

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```

351  TGTGCGCCCTT  TTGTCTTTGG  CGCTGGTAAA  CCATATGAAT  TTTCTATTGA
    ACAGCGGGAA  AACAGAAACC  GCGACCATTT  GGTATACCTA  AAAGATAACT

401  TTGTGACAAA  ATAAACTTAT  TCCGTGGTGT  CTTTGCGTTT  CTTTATATAG
    AACACTGTTT  TATTGAATA  AGCACCCACA  GAAACGCCAA  GAAAATATAC

451  TTGCCACCTT  TATGTATGTA  TTTTCTACGT  TTGCTAACAT  ACTGCGTAAT
    AACGGTGGAA  ATACATACAT  AAAAGATGCA  AACGATTGTA  TGACGCATTA

                                HindIII
                                ~~~~~

501  AAGGAGTCTT  GATAAGCTTG  ACCTGTGAAG  TGAAAAATGG  CGCAGATTGT
    TTCCCTCAGAA  CTATTCGAAC  TGGACACTTC  ACTTTTACC  GCGTCTAACA

                                PacI
                                ~~~~~

551  GCGACATTTT  TTTTGTCTGC  CGTTTAATTA  AAGGGGGGGG  GGGCCCGGCC
    CGCTGTAAA  AAAACAGACG  GCAAATTAAT  TTCCCCCCCC  CCCC GGCCGG

                                BsrGI
                                ~~~~~

601  TGGGGGGGGG  TGTACATGAA  ATTGTAAACG  TTAATATTTT  GTTAAAATTC
    ACCCCCCCCC  ACATGTACTT  TAACATTGTC  AATTATAAAA  CAATTTTAAG

```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```

651  GCGTTAAATT TTTGTTAAAT CAGCTCATTT TTTAACCAAT AGGCCGAAAT
    CGCAATTATA AACAAATTA GTCGAGTAAA AAATTGGTTA TCCGGCTTTA

701  CGGCAAAATC CCTTATAAAT CAAAAGAATA GACCGAGATA GGGTTGAGTG
    GCCGTTTATG GGAATATTA GTTTTCTTAT CTGGCTCTAT CCCAACTCAC

751  TTGTTCCAGT TTGGAACAAG AGTCCACTAT TAAAGAACGT GGAATCCAAC
    AACAAAGTCA AACCTTGTC TCAGGTGATA ATTTCTTGCA CTTGAGGTG

801  GTCAAAGGCG GAAAACCGT CTATCAGGC GATGGCCAC TACGAGAACC
    CAGTTTCCCG CTTTTTGGCA GATAGTCCCG CTACCGGGTG ATGCTCTTGG

851  ATCACCCCTAA TCAAGTTTTT TGGGTCGAG GTGCCGTAAA GCACTAAATC
    TAGTGGGATT AGTTCAAAAA ACCCCAGCTC CACGGCATTT CGTGATTTAG

                                BanII
                                ~~~~~

901  GGAACCCCTAA AGGAGCCCC CGATTTAGAG CTTGACGGGG AAAGCCGGCG
    CCTTGGGATT TCCCTCGGGG GCTAAATCTC GAACTGCCCC TTTCGGCCGC

951  AACGTGGCGA GAAAGGAAGG GAAGAAAGCG AAAGGAGCGG GCGCTAGGGC
    TTGCACCGCT CTTTCCTTCC CTTCTTTTCG TTTCTCTCGC CGCGATCCCC

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1001 GCTGGCAAGT GTAGGGTCA CGCTGGCGGT AACCAACACA CCCGCCGCCG  
CGACCGTTCA CATCGCCAGT GCGACGCGCA TTGGTGTGT GGGCGGCCG

}
}
}
}
}
}

1051  
TTAATGCGCC GCTACAGGC GCGTGCTAGC CATGTGAGCA AAAGGCCAGC  
AATTACGCGG CGATGTCCCG CGACCGATCG GTACACTCGT TTTCGGGTCG

1101  
AAAAGGCCAG GAACCGTAAA AAGGCCGGT TGCTGGCGTT TTTCATAGG  
TTTTCCGGTC CTTGGCATT TTCCGGCGCA ACGACCGCAA AAAGGTATCC

1151  
CTCCGCCCC CTGACGAGCA TCACAAAAT CGACGCTCAA GTCAGAGGTG  
GAGCGGGGG GACTGCTCGT AGTGTTTTTA GCTGCGAGTT CAGTCTCCAC

1201 GCGAAACCCG ACAGGACTAT AAAGATACCA GGCGTTTCCC CCTGGAAGCT  
CGCTTTGGGC TGTCC TGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA

2  
2  
2  
2  
2  
2

1251 CCTCGTGCG CTCTCCTGTT CCGACCTGC CGCTTACCGG ATACCTGTCC  
GGGAGCACGC GAGAGGACAA GCTGGGACG GCGAATGGCC TATGGACAGG

1301 GCCTTTCTCC CTTCGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG  
CGGAAAGAGG GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```
1351  GTATCTCAGT  TCGGTGTAGG  TCGTTCGCTC  CAAGCTGGGC  TGTGTGCACG
      CATAGAGTCA  AGCCACATCC  AGCAAGCGAG  GTTCGACCCG  ACACACGTGC

1401  AACCCCCCGT  TCAGCCCCGAC  CGCTGGGCCT  TATCCGGTAA  CTATCGTCTT
      TTGGGGGGCA  AGTCGGGCTG  GCGACGCGGA  ATAGGCCATT  GATAGCAGAA

1451  GAGTCCAACC  CGGTAAGACA  CGACTTATCG  CCACTGGCAG  CAGCCACTGG
      CTCAGGTGG  GCCATTCTGT  GCTGAATAGC  GGTGACCCGC  GTCGGTGACC

1501  TAACAGGATT  AGCAGAGCGA  GGTATGTAGG  CCGTGCTACA  GAGTCTTGA
      ATTGTCCTAA  TCGTCTCGCT  CCATACATCC  GCCACGATGT  CTCAAGAACT

1551  AGTGGTGGCC  TAACTACGGC  TACACTAGAA  GAACAGTATT  TGGTATCTGC
      TCACCACCGG  ATTGATGCCG  ATGTGATCTT  CTTGTCAATA  ACCATAGACG

1601  GCTCTGCTGT  AGCCAGTTAC  CTTCGGAAAA  AGAGTTGGTA  GCTCTTGATC
      CGAGACGACA  TCGGTCAATG  GAAGCCTTTT  TCTCAACCAT  CGAGAACTAG

1651  CGGCAAAACA  ACCACCGCTG  GTAGCGGTGG  TTTTTTTGT  TGCAAGCAGC
      GCCGTTTGTT  TGGTGGCGAC  CATCGCCACC  AAAAAACAA  ACGTTCGTGC

1701  AGATTACGCG  CAGAAAAAAA  GGATCTCAAG  AAGATCCTTT  GATCTTTTCT
      TCTAATGCGC  GTCCTTTTTT  CCTAGAGTTC  TTCTAGGAAA  CTAGAAAAAG
```

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```

1751  ACGGGGTCTG  ACGCTCAGTG  GAACGAAAC  TCACGTTAAG  GGATTTTGGT
      TGCCCCAGAC  TGCAGTCAC  CTTGCTTTG  AGTGCAATTC  CCTAAACCA

      BglII
      ~~~~~
1801  CAGATCTAGC  ACCAGCGGTT  TAAGGCACC  AATAACTGCC  TTAAAAAAT
      GTCTAGATCG  TGGTCCGCAA  ATTCCCGTGG  TTATTGACGG  AATTTTTTA

1851  TACGCCCCGC  CCTGCCACTC  ATCGCAGTAC  TGTGTAAAT  CATTAAGCAT
      ATGCGGGGCG  GGACGGTGAG  TAGCGTCATG  ACAACATTAA  GTAATTTCGA

1901  TCTGCCGACA  TGGAAGCCAT  CACAAACGGC  ATGATGAACC  TGAATCGCCA
      AGACGGCTGT  ACCTTCGGTA  GTGTTTGCCG  TACTACTTGG  ACTTAGCGGT

1951  GCGGCATCAG  CACCTTGTCG  CCTTGCGTAT  AATATTTGCC  CATAGTGAAA
      CGCCGTAGTC  GTGGAACAGC  GGAACGCATA  TTATAAACGG  GTATCACTTT

2001  ACGGGGGCGA  AGAAGTTGTC  CATATTGGCT  ACGTTTAAAT  CAAAACCTGGT
      TGCCCCCGCT  TCTTCAACAG  GTATAACCGA  TGCAAATTTA  GTTTGACCA

2051  GAAACTCACC  CAGGGATTGG  CTGAGACGAA  AAACATATTC  TCAATAAACCC
      CTTTGAGTGG  GTCCCTAACC  GACTCTGCTT  TTTGTATAAG  AGTTATTTGG

```

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Figure 35: functional map and sequence of modular vector pCAL4 (continued)

|      |   |
|------|---|
| 2101 | CTTTAGGGAA ATAGGCCAGG TTTTCACCGT AACACGCCAC ATCTTGCGAA<br>GAAATCCCTT TATCCGGTCC AAAAGTGGCA TTGTGCGGTG TAGAACGCTT  |
| 2151 | TATATGTGTA GAAACTGCCG GAAATCGTCG TGGTATTCAC TCCAGAGCGA<br>ATATACACAT CTTTGACGGC CTTTAGCAGC ACCATAAGTG AGGTCTCGCT  |
| 2201 | TGAAAACGTT TCAGTTTGCT CATGGA AAC GGTGTAACAA GGTGAACAC<br>ACTTTTGCAA AGTCAAACGA GTACCTTTTG CCACATTGTT CCCACTTGTG   |
| 2251 | TATCCCATAT CACCAGCTCA CCGTCTTTCA TTGCCATACG GAACTCCGGG<br>ATAGGGTATA GTGGTCGAGT GGCAGAAAGT AACGGTATGC CTTGAGGCC   |
| 2301 | TGAGCATTC A TCAGCGGGC AAGAATGTGA ATAAAGGCCG GATAAAACTT<br>ACTCGTAAGT AGTCCGCCCG TTCTTACACT TATTTCCGGC CTATTTTGAA  |
| 2351 | GTGCTTATTT TTCTTTACGG TCTTTAAAAA GCCCGTAATA TCCAGCTGAA<br>CACGAATAAA AAGAAATGCC AGAAATTTT CCGGCATTAT AGGTCGACTT   |
| 2401 | CGGTCCTGGT ATAGGTACAT TGAGCAACTG ACTGAAATGC CTCAAAATGT<br>GCCAGACCAA TATCCATGTA ACTCGTTGAC TGACTTTACG GAGTTTTACA  |
| 2451 | TCCTTACGAT GCCATTGGGA TATATCAACG GTGGTATATC CAGTGATTTT<br>AGAAATGCTA CGGTAACCCCT ATATAGTTGC CACCATATAG GTCACATAAA |

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

```

2501  TTTCTCCATT  TTAGCTTCCT  TAGCTCCTGA  AAATCTCGAT  AACTCAAAAA
      AAAGAGGTAA  AATCGAAGGA  ATCGAGGACT  TTTAGAGCTA  TTGAGTTT
2551  ATACGCCCGG  TAGTGATCTT  ATTTCAATTAT  GTGAAAGTT  GGAACCTCAC
      TATCGGGGCC  ATCACTAGAA  TAAAGTAATA  CCACTTTCAA  CCTTGGAGTG

      AatII
      ~~~~~
2601  CCGACGTCTA  ATGTGAGTTA  GCTCACTCAT  TAGGCACCCC  AGGCTTTACA
      GGCTGCAGAT  TACACTCAAT  CGAGTGAGTA  ATCCGTGGGG  TCCGAAATGT
2651  CTTTATGCTT  CCGGCTCGTA  TGTGTGTGG  AATTGTGAGC  GGATAACAAT
      GAAATACGAA  GGCCGAGCAT  ACAACACACC  TTAACACTCG  CCTATTGTTA

      XbaI   SphI
      ~~~~~
2701  TTCACACAGG  AAACAGCTAT  GACCATGATT  ACGAATTCTT  AGAGCATGCG
      AAGTGTGTCC  TTTGTGCGATA  CTGGTACTAA  TGCTTAAAGA  TCTCGTACGC

      EcoRI

2751  GGGGG
      CCCCC

```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors

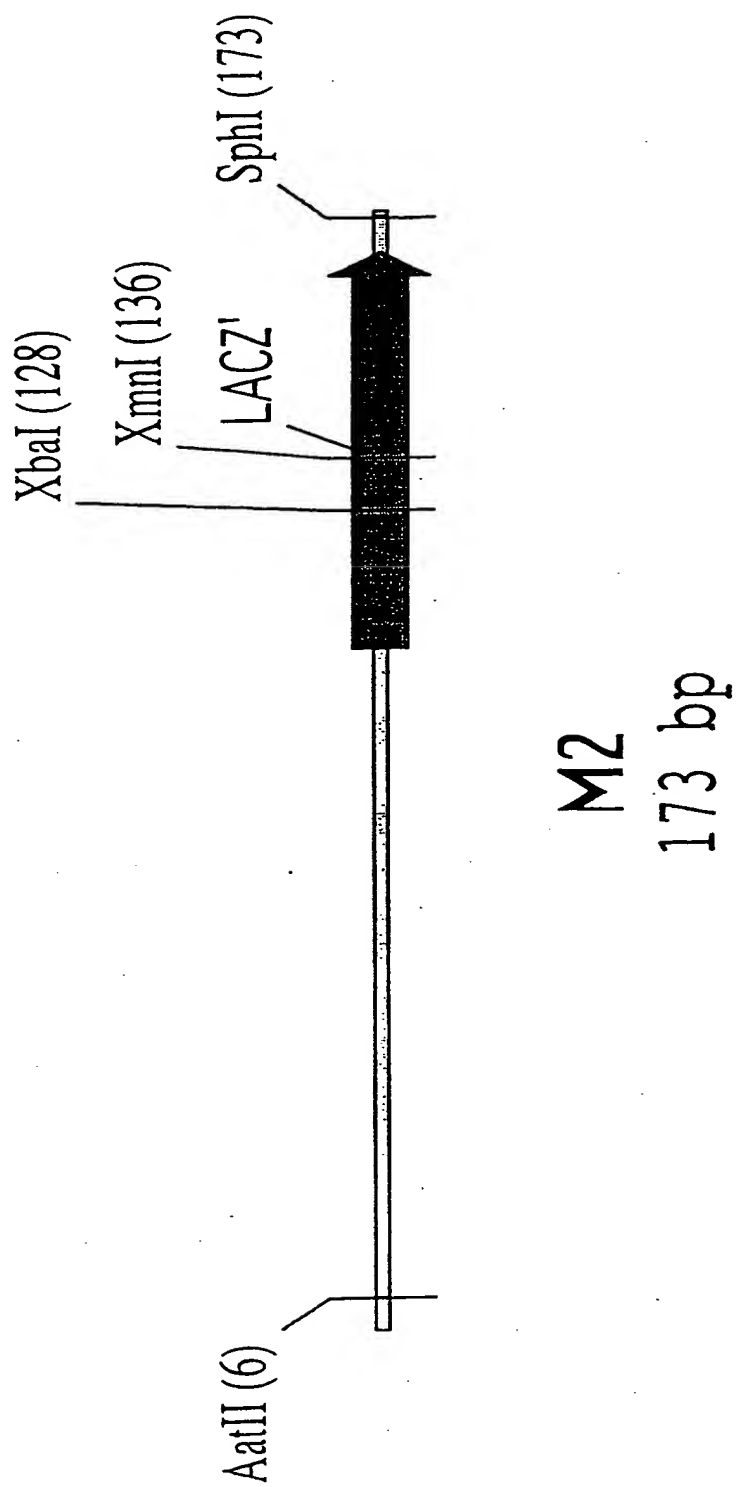
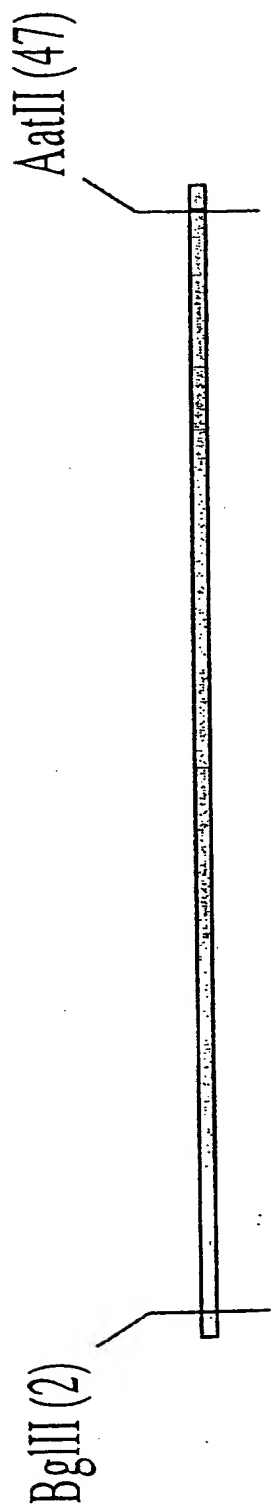


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



M3  
47 bp

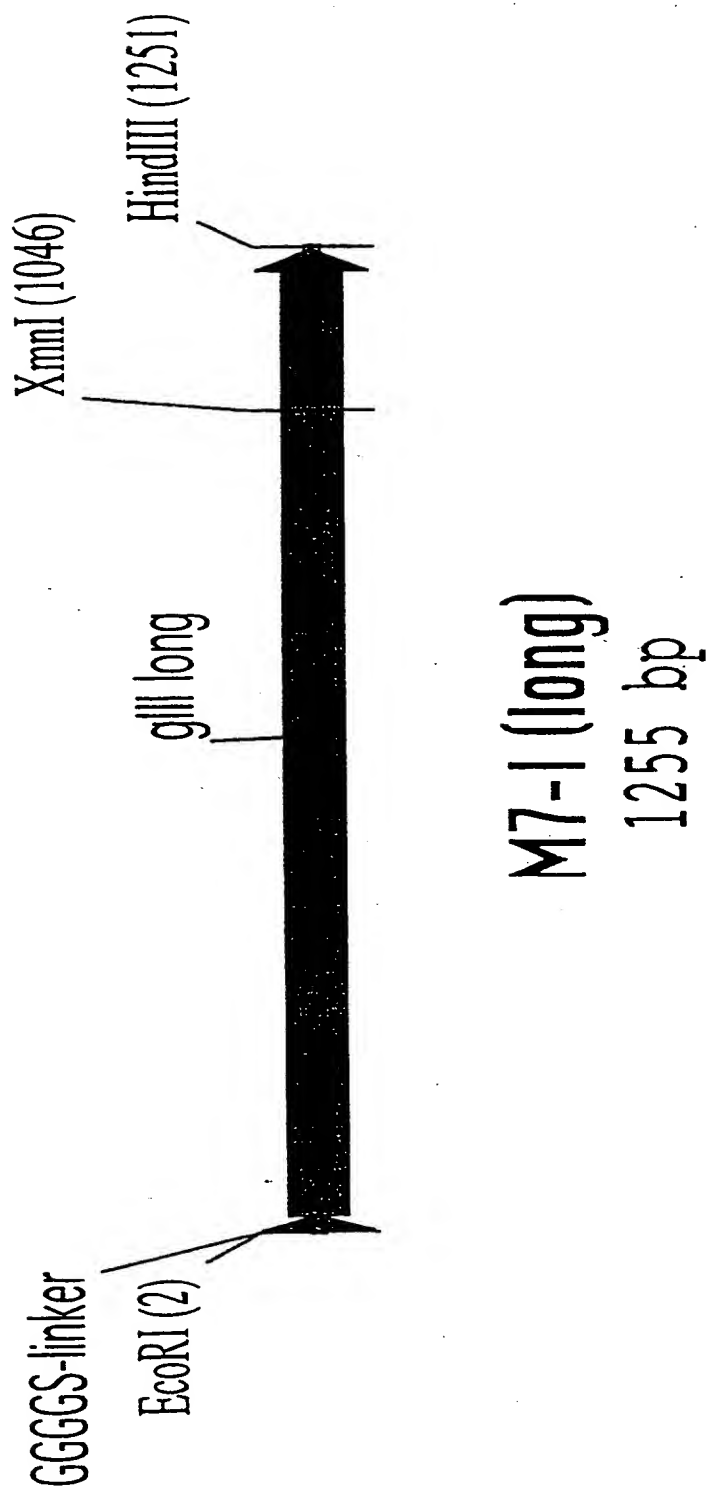
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 3:

|   | BglII   | AatII |
|---|---|-------|
|   | -----   | ----- |
| 1 | AGATCTCATA ACTTCGTATA ATGTATGCTA TACGAAGTTA TGACGTC |       |
|   | TCTAGAGTAT TGAAGCATAT TACATACGAT ATGCTTCAAT ACTGCAG |       |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

## M 7-I (long):

ECORI  
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```

1  GAATTCGGTG GTGGTGGATC TCGGTGCGCT GAAACGGTTG AAAGTTGTTT
   CTTAAGCCAC CACCACCTAG ACGCACGCCA CTTTGCCAAC TTTCACACAAA

51 AGCAAAATCC CATAAGAAA ATTCATTTAC TAACGTCTGG AAAGACGACA
   TCGTTTTAGG GTATGTCTTT TAAGTAAATG ATTGCAGACC TTTCTGCTGT

101 AACTTTAGA TCGTTACGCT AACTATGAGG GCTGCTGTG GAATGCTACA
   TTTGAAATCT AGCAATGCCA TTGATACTCC CGACAGACAC CTTACGATGT

151 GCGGTTGTAG TTTGTACTGG TGACGAAACT CAGTGTTAGG GTACATGGGT
   CCGCAACATC AAACATGACC ACTGCTTTGA GTCACAATGC CATGTACCCA

201 TCCTATTGGG CTTGCTATCC CTGAAAATGA GGGTGGTGGC TCTGAGGGTG
   AGGATAACCC GAACGATAGG GACTTTTACT CCCACCACCG AGACTCCCAC

251 GCGGTTCTGA GGGTGGCGGT TCTGAGGGTG GCGGTACTAA ACCTCCTGAG
   CGCCAAGACT CCCACCGCCA AGACTCCCAC CGCCATGATT TGGAGGACTC

301 TACGGTGATA CACCTATTCC GGGCTATACT TATATCAACC CTCTCGACGG
   ATGCCACTAT GTGGATAAGG CCCGATATGA ATATAGTTGG GAGAGCTGCC

```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |             |             |            |             |             |
|-----|-------------|-------------|------------|-------------|-------------|
| 351 | CACTTATCCG  | CCTGGTACTG  | AGCAAAACCC | CGCTAATCCT  | AATCCTTCTC  |
|     | GTGAATAGGC  | GGACCATGAC  | TCGTTTGGG  | GCGATTAGGA  | TTAGGAAGAG  |
| 401 | TTGAGGAGTC  | TCAGCCCTCTT | AATACTTTCA | TGTTTCAGAA  | TAATAGGTTC  |
|     | AACTCCCTCAG | AGTCGGAGAA  | TTATGAAAGT | ACAAAGTCTT  | ATTATCCAAG  |
| 451 | CGAAATAGGC  | AGGGGGCATT  | AACTGTTTAT | ACGGGCACCTG | TTACTCAAGG  |
|     | GCTTTATCCG  | TCCCCCGTAA  | TTGACAAATA | TGCCCCGTGAC | AATGAGTTCC  |
| 501 | CACTGACCCC  | GTTAAAACTT  | ATTACCAGTA | CATCCTGTGA  | TCATCAAAAG  |
|     | GTGACTGGGG  | CAATTTTGAA  | TAATGGTCAT | GTGAGGACAT  | AGTAGTTTTC  |
| 551 | CCATGTATGA  | CGCTTACTGG  | AACGGTAAAT | TCAGAGACTG  | CGCTTTCCAT  |
|     | GGTACATACT  | GCGAATGACC  | TTGCCATTTA | AGTCTCTGAC  | GCGAAAGGTA  |
| 601 | TCTGGGCTTTA | ATGAGGATTT  | ATTGTTTGT  | GAATATCAAG  | GCCAAATCGTC |
|     | AGACCGAAAT  | TACTCCTAAA  | TAAACAAACA | CTTATAGTTC  | CGGTTAGCAG  |
| 651 | TGACCTGCCT  | CAACCTCCTG  | TCAATGCTGG | CGGCGGCTCT  | GGTGGTGGTT  |
|     | ACTGGACGGA  | GTGGAGGAC   | AGTTACGACC | GCCGCCGAGA  | CCACCACCAA  |
| 701 | CTGGTGCGCG  | CTCTGAGGGT  | GGTGGCTCTG | AGGGTGGCGG  | TTCTGAGGGT  |
|     | GACCACCGCC  | GAGACTCCCA  | CCACCGAGAC | TCCCACCGCC  | AAGACTCCCA  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```

751  GCGGCTCTG AGGAGGCGG TTCCGGTGGT GGCTCTGGTT CCGGTGATTT
    CCGCCGAGAC TCCCTCCGCC AAGGCCACCA CCGAGACCAA GGCCACTAAA

801  TGATTATGAA AAGATGGCAA ACGCTAATAA GGGGGCTATG ACCGAAAATG
    ACTAATACTT TTCTACCGTT TCGGATTATT CCCCCGATAC TGGCTTTTAC

851  CCGATGAAAA CGCGCTACAG TCTGACGCTA AAGGCAAACT TGATTCTGTC
    GGCTACTTTT GCGCGATGTC AGACTGCGAT TTCCCGTTGA ACTAAGACAG

901  GCTACTGATT ACGGTGCTGC TATCGATGGT TTCATTGGTG ACGTTTCCGG
    CGATGACTAA TGCCACGACG ATAGCTACCA AAGTAACCAC TGCAAAGGCC

951  CCTTGCTAAT GGTAATGGTG CTA CTGGTGA TTTTGCTGGC TCTAATTCCC
    GGAACGATTA CCATTACCAC GATGACCACT AAAACGACCG AGATTAAAGG

                                XmnI
                                -----
1001  AAATGGCTCA AGTCGGTGAA GGTGATAATT CACCTTTAAT GAATAATTTC
    TTACCGAGT TCAGCCACTT CCACTATTAA GTGGAAATTA CTTATTAAAG

1051  CGTCAATATT TACCTTCCAT CCCTCAATCG GTTGAATGTC GCCCTTTTGT
    GCAGTTATAA ATGGAAGGTA GGGAGTTAGC CAACTTACAG CGGGAAAACA

```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 2:

|     |             |            |                                  |
|-----|-------------|------------|----------------------------------|
|     | AatII       |            |                                  |
|     | ~~~~~       |            |                                  |
| 1   | GACGTCCTTAA | TGTGAGTTAG | CTCACTCATT AGGCACCCCA GGCTTTACAC |
|     | CTGCAGAAAT  | ACACTCAATC | GAGTGAGTAA TCCGTGGGT CCGAAATGTG  |
| 51  | TTTATGCTTC  | CGGCTCGTAT | GTTGTGTGA ATTGTGAGCG GATAACAATT  |
|     | AAATACGAAG  | GCCGAGCATA | CAACACACCT TAACACTCGC CTATTGTTAA |
|     |             |            | XmnI                             |
|     |             |            | ~~~~~                            |
|     |             |            | XbaI                             |
|     |             |            | ~~~~~                            |
| 101 | TCACACAGGA  | AACAGCTATG | ACCATGTCTA GAATAACTTC GTATAATGTA |
|     | AGTGTGTCCT  | TTGTCGATAC | TGGTACAGAT CTTATTGAAG CATATTACAT |
|     |             |            | SphI                             |
|     |             |            | ~~~~~                            |
| 151 | CGCTATACGA  | AGTTATCGCA | TGC                              |
|     | GCGATATGCT  | TCAATAGCGT | ACG                              |



Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

1101 CTTTGGCGCT GGTAACCCCT ATGAATTTC TATTGATTGT GACAAAATAA  
GAAACCGCGA CCATTGGGA TACTTAAAG ATAACATAACA CTGTTTTATT

1151 ACTTATTCCG TGGTGTCTTT GCGTTTCTTT TATATGTTGC CACCTTTATG  
TGAATAAGGC ACCACAGAAA CGCAAAGAAA ATATACAACG GTGGAAATAC

1201 TATGTATTTT CTACGTTTGC TAACATACTG CGTAATAAGG AGTCTTGATA  
ATACATAAAA GATGCAAACG ATTGTATGAC GCATTATTCC TCAGAACTAT

HindIII

HindI

----

1251 AGCTT  
TCGAA

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

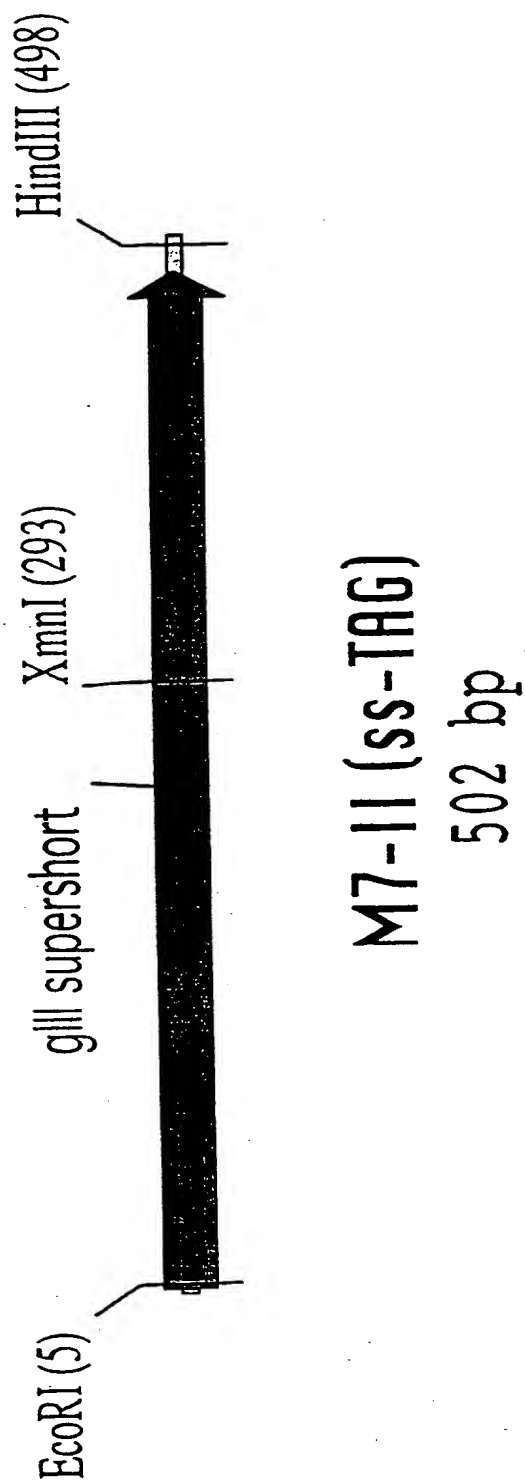


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

## M 7-II (ss-TAG) :

ECORI

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|     |             |            |            |            |            |
|-----|-------------|------------|------------|------------|------------|
| 1   | CGGGAATTCTG | GAGGCGGTTC | CGGTGGTGGC | TCTGGTTCCG | GTGATTTTGA |
|     | GCCCTTAAGC  | CTCCGCCAAG | GCCACCACCG | AGACCAAGGC | CACTAAAACT |
| 51  | TTATGAAAAG  | ATGGCAAACG | CTAATAAGGG | GGCTATGACC | GAAAATGCCG |
|     | AATACTTTC   | TACCGTTTC  | GATTATTCCC | CCGATACTGG | CTTTTACGGC |
| 101 | ATGAAAACGC  | GCTACAGTCT | GACGCTAAAG | GCAAACCTGA | TTCTGTGCGT |
|     | TACTTTTGGC  | CGATGTCAGA | CTGCGATTTC | CGTTTGAACT | AAGACAGCGA |
| 151 | ACTGATTACG  | GTGCTGCTAT | CGATGGTTTC | ATTGGTGACG | TTTCCGGCCT |
|     | TGACTAATGC  | CACGACGATA | GCTACCAGAG | TAACCACTGC | AAAGGCCGGA |
| 201 | TGCTAATGGT  | AATGGTGCTA | CTGGTGATT  | TGCTGGCTCT | AATCCCCAAA |
|     | ACGATTACCA  | TTACCACGAT | GACCACTAAA | ACGACCGAGA | TTAAGGGTTT |
| 251 | TGGCTCAAGT  | CGGTGACGGT | GATAATCAC  | CTTAAATGAA | TAATTTCCGT |
|     | ACCGAGTTCA  | GCCACTGCCA | CTATTAAGTG | GAAATTACTT | ATTAAAGGCA |

XmnI

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```

301  CAATATTAC  CTTCCCTCCC  TCAATCGGTT  GAATGTCGCC  CTTTGTCTT
      GTTATAAATG  GAAGGAGGG  AGTAGCCAA  CTTACAGCGG  GAAACAGAA

351  TGGCGCTGGT  AAACCATATG  AATTCTCTAT  TGATTGTGAC  AAAATAAACT
      ACCGCGACCA  TTTGGTATAC  TTAAAGATA  ACTAACACTG  TTTTATTGA

401  TATCCCGTGG  TGTCTTTGCG  TTTCTTTTAT  ATGTTGCCAC  CTTTATGTAT
      ATAAGGCACC  ACAGAAACGC  AAAGAAAATA  TACAACGGTG  GAAATACATA

      HindIII
      ----

451  GTATTTCTA  CGTTTGCTAA  CATACTGCCGT  AATAAGGAGT  CTTGATAAGC
      CATAAAGAT  GCAACGATT  GTATGACGCA  TTATTCCTCA  GAACTATTCG

501  Hi
      ~
      TT
      AA

```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

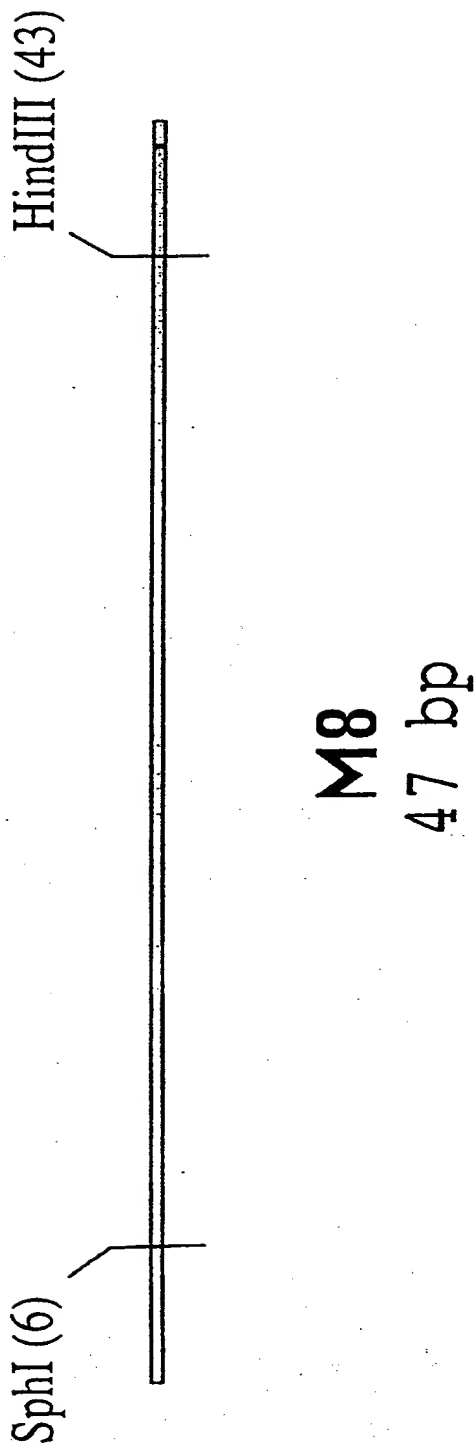


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 8:

|   | SphI  | HindIII |
|---|---|---------|
|   | ~~~~~   | ~~~~~   |
| 1 | GCATGCCATA ACTTCGTATA ATGTACGCTA TACGAAGTTA TAAGCTT | TAAGCTT |
|   | CGTACGGTAT TGAAGCATAT TACATGCGAT ATGCTTCAAT ATTCGAA | ATTCGAA |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

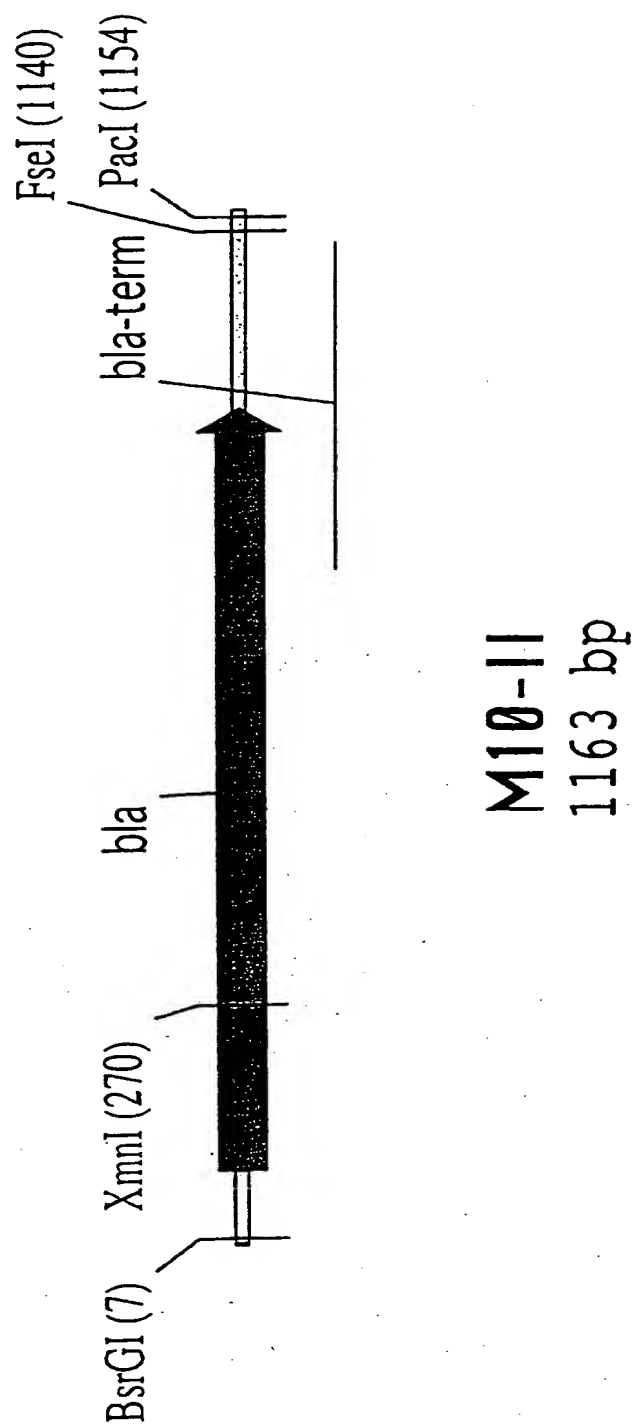


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

## M 10-II:

BsrGI

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```

1  GGGGGTGATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCTGATA
   CCCCCACATG TAAGTTTATA CATAGGCGAG TACTCTGTTA TTGGGACTAT

51  AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTC
   TTACGAAGTT ATTATAACTT TTTCCCTTCTC ATACTCATAA GTTGTAAGG

101 GTGTCGCCCT TATTCCTTT TTTGCGGCAT TTTGCCCTCC TGTTTTTGCT
   CACAGCGGGA ATAAGGGAAA AAACGCCGTA AAACGGAAGG ACAAAAACGA

151 CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAGGATC AGTTGGGTGC
   GTGGGTCTTT GCGACCACTT TCATTTTCTA CGACTCCTAG TCAACCCACG

201 GCGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA
   CGCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCATTC TAGGAACTCT

```

XmnI

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251 GTTTTCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT TAAAGTTCTG
   CAAAAGCGGG GCTTCTTGCA AAAGGTTACT ACTCGTGAAA ATTTCAAGAC

```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

301 CTATGTGGCG CCGTATTATC CCGTATTGAC GCCGGGCAAG AGCAACTCGG  
GATACACCGC GCCATAATAG GGCATAACTG CGGCCCGTTC TCGTTGAGCC

351 TCGCCGCATA CACTATTCTC AGAATGACTT GGTGAGTAC TCACCAGTCA  
AGCGGCGTAT GTGATAAGAG TCTTACTGAA CCAACTCATG AGTGGTCAGT

401 CAGAAAAGCA TCTTACGGAT GGCA TGACAG AATT ATGCAGTGCT  
GTCTTTTCGT AGAATGCCCTA CCGTACTGTC ATTCTCTTAA TACGTCACGA

451 GCCATAACCA TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT  
CGGTATTGGT ACTCACTATT GTGACGCCCG TTGAATGAAG ACTGTTGCTA

501 CGGAGGACCG AAGGAGCTAA CCGCTTTTTC GCACAACATG GGGGATCATG  
GCCTCCTGGC TTCCTCGATT GCGGAAAAAA CGTGTGTAC CCCCTAGTAC

551 TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC CATAACCAAC  
ATTGAGCGGA ACTAGCAACC CTGCGCCTCG ACTTACTTTC GTATGGTTTG

601 GACGAGCGTG ACACCACGAT GCCTGTAGCA ATGGCAACAA CGTTGCCGCA  
CTGCTCGCAC TGTGGTGCTA CGGACATCGT TACCGTTGTT GCAACGCCGTT

651 ACTATTAACT GCGAACTAC TTA CTCTAGC TTCCCGGCAA CAGTTAATAG  
TGATAATTGA CCGCTTGATG AATGAGATCG AAGGCCCGTT GTCAATTATC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |            |             |             |             |            |
|------|------------|-------------|-------------|-------------|------------|
| 701  | ACTGGATGGA | GGCGGATAAA  | GTTGCAGGAC  | CACCTTCTGCG | CTCGGCCCTT |
|      | TGACCTACCT | CCGCCTATTT  | CAACGTCCCTG | GTGAAGACGC  | GAGCCGGGAA |
| 751  | CCGGCTGGCT | GGTTTATTGC  | TGATAAATCT  | GGAGCCGGTG  | AGCGTGGGTC |
|      | GGCCGACCGA | CCAAATAACG  | ACTATTTAGA  | CCTCGGCCAC  | TCGCACCCAG |
| 801  | TCGCGGTATC | ATTGCAGCAC  | TGGGGCCAGA  | TGGTAAGCCC  | TCCCGTATCG |
|      | AGCGCCATAG | TAAACGTCGTG | ACCCCGGTCT  | ACCATTCGGG  | AGGCATAGC  |
| 851  | TAGTTATCTA | CACGACGGGG  | AGTCAGGCAA  | CTATGGATGA  | ACGAAATAGA |
|      | ATCAATAGAT | GTGCTGCCCC  | TCAGTCCGTT  | GATACCTACT  | TGCTTTATCT |
| 901  | CAGATCGCTG | AGATAGGTGC  | CTCACTGATT  | AAGCATTTGG  | TAACTGTCAG |
|      | GTCTAGCGAC | TCTATCCACG  | GAGTGACTAA  | TTCGTAACCC  | ATTGACAGTC |
| 951  | ACCAAGTTTA | CTCATATATA  | CTTTAGATTG  | ATTTAAACT   | TCATTTTAA  |
|      | TGGTTCAAAT | GAGTATATAT  | GAAATCTAAC  | TAAATTTTGA  | AGTAAATAAT |
| 1001 | TTTAAAGGA  | TCTAGGTGAA  | GATCCTTTT   | GATAATCTCA  | TGACCAAAT  |
|      | AAATTTTCCT | AGATCCACTT  | CTAGGAAAAA  | CTATTAGAGT  | ACTGGTTTAA |
| 1051 | CCCTTAACGT | GAGTTTTCGT  | TCCACTGAGC  | GTCAGACCCC  | GTAGAAAAGA |
|      | GGGAATTGCA | CTCAAAAGCA  | AGTGACTCG   | CAGTCTGGGG  | CATCTTTTCT |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |            | FseI       | PacI      |            |             |
|------|------------|------------|-----------|------------|-------------|
| 1101 | TCAAAGGATC | TTCTTGAGAT | CCTTTTGAT | AATGGCCGGC | CCCCCCCCCTT |
|      | AGTTCCCTAG | AAGAACTCTA | GGAAAACTA | TTACCGGCCG | GGGGGGGGAA  |

|      |           |     |
|------|-----------|-----|
| 1151 | AATAAGGG  | GGG |
|      | TTAATCCCC | CCC |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

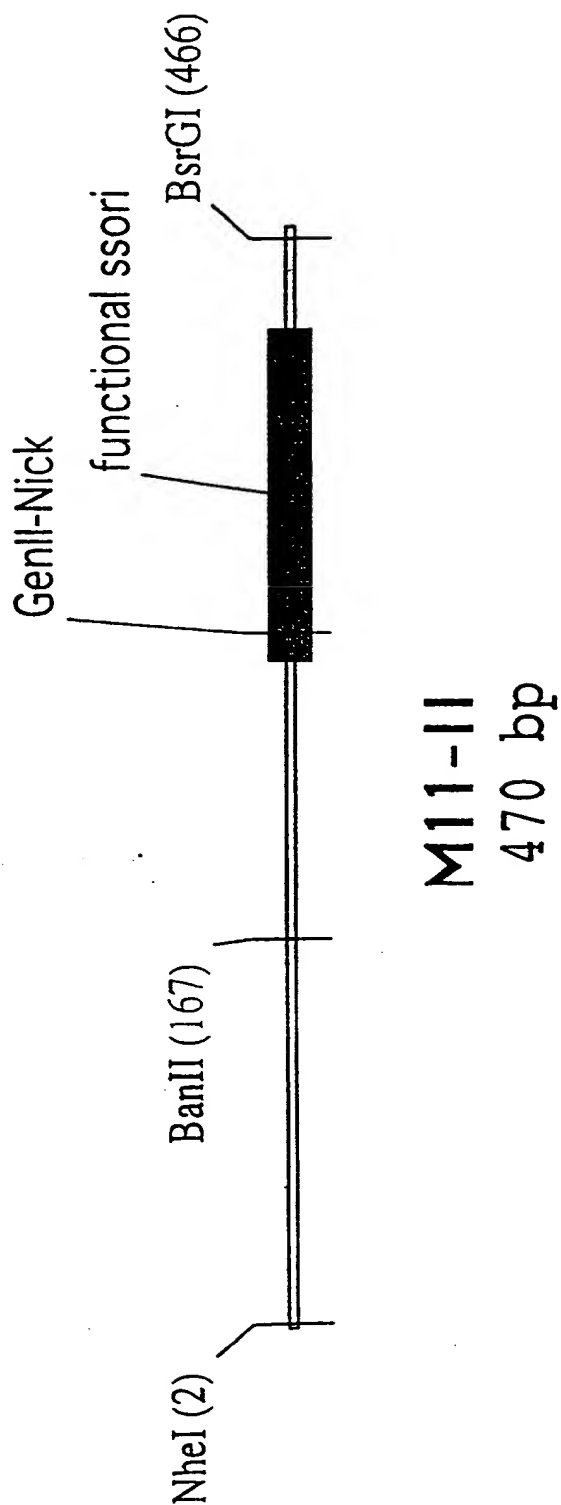


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

## M11-II:

## NheI

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```

1  GCTAGCACGC GCCCTGTAGC GCGCATTAAG GCGGGCGGGG TGTGGTGGTT
   CGATCGTGCG CCGGACATCG CCGCGTAATT CCGCCGCCCC ACACCACCAA

51  ACGCGCAGCG TGACCGCTAC ACTTGCCAGC GCCCTAGCGC CCGCTCCTTT
   TCGCGGTCGC ACTGGCGATG TGAACGGTCG CCGGATCGCG GCGGAGGAAA

101 CGCTTCTTTC CCTTCCCTTC TCGCCACGTT CGCGGGCTTT CCCCCTCAAG
   GCGAAAGAAG GGAAGGAAAG AGCGGTGCAA CCGGCCGAAA GGGCAGTTC

```

## BanII

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151 CTCTAAATCG GGGCTCCCTT TTAGGGTTCC GATTAGTGC TTACGGCAC
   GAGATTAGC CCGGAGGGA AATCCCAAGG CTAAATCACG AATGCCCGTG

201 CTCGACCCCA AAAAATTGA TTAGGGTGAT GGTCTCGTA GTGGGCCATC
   GAGCTGGGGT TTTTGAACCT AATCCCACTA CCAAGAGCAT CACCCGGTAG

251 GCCCTGATAG ACGGTTTTC GCCCTTTGAC GTTGGAGTCC ACGTTCTTTA
   CGGGACTATC TGCCAAAAG CGGAAACTG CAACCTCAGG TGCAAGAAAT

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```
301  ATAGTGGACT CTTGTTCCAA ACTGGAACAA CACTCAACCC TATCTCGGTC
    TATCACCTGA GAACAAGGTT TGACCTTGTT GTGAGTTGGG ATAGAGCCAG

351  TATTCTTTGG ATTTATAAGG GATTTGCCG ATTTCGGCCT ATTGGTTAAA
    ATAAGAAAAC TAAATATTCC GTAAACGGC TAAAGCCGGA TAACCAATTT

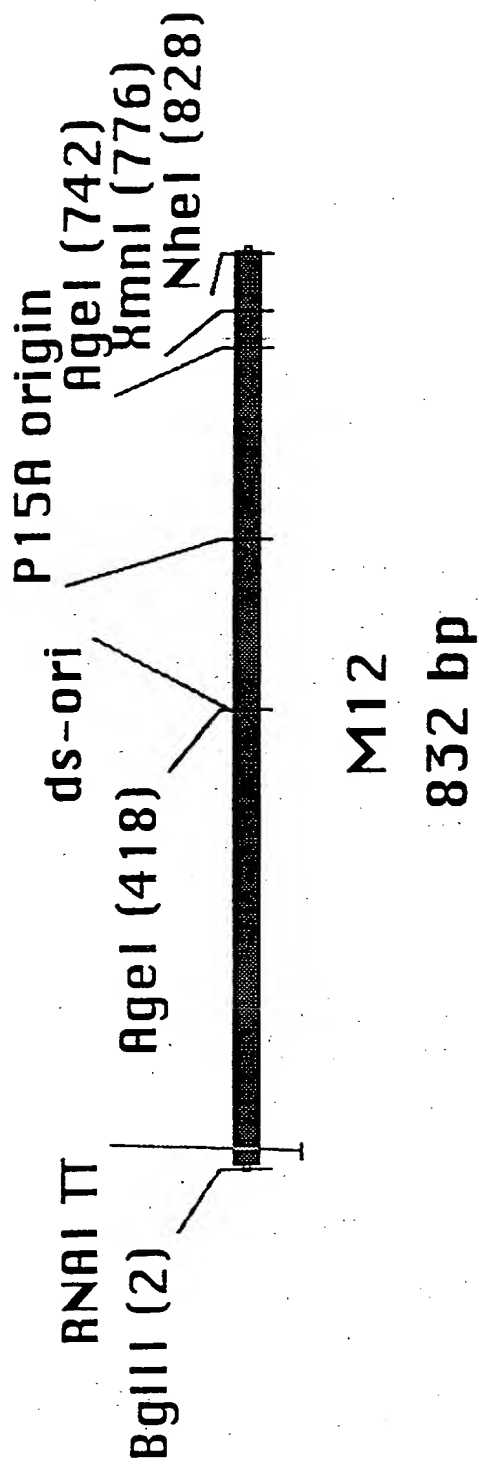
401  AAATGAGCTG ATTTAACAAA AATTAAACGC GAATTTTAAAC AAAATATTAA
    TTTACTCGAC TAAATTGTTT TTAATTTGCG CTTAAAAATTG TTTTATAATT

                                BsrGI
                                ~~~~~

451  CGTTTACAAT TTCATGTACA
    GCAAATGTTA AAGTACATGT
```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|       |                                                        |       |             |
|-------|--------------------------------------------------------|-------|-------------|
| M 12: |                                                        | BgIII |             |
|       |                                                        | ~~~~~ |             |
| 1     | AGATCTAATA AGATGATCTT CTTGAGATCG TTTTGGTCTG CGCGTAATCT |       | GCGCATTAGA  |
|       | TCTAGATTAT TCTACTAGAA GAACTCTAGC AAAACCAGAC            |       |             |
| 51    | CTTGCTCTGA AAACGAAAA ACCGCTTGC AGGGCGGTTT TTCGTAGGTT   |       | AAGCATCCAA  |
|       | GAACGAGACT TTTGCTTTT TGGCGGAACG TCCCGCCAAA             |       |             |
| 101   | CTCTGAGCTA CCAACTCTTT GAACCGAGGT AACTGGCTTG GAGGAGCGCA |       | CTCCTCGCGT  |
|       | GAGACTCGAT GGTGAGAAA CTTGGCTCCA TTGACCGAAC             |       |             |
| 151   | GTCACTAAAA CTGTCCCTTT CAGTTTAGCC TTAACCGGCG CATGACTTCA |       | GTACTGAAAGT |
|       | CAGTGATTTT GAACAGGAAA GTCAAATCGG AATTGGCCGC            |       |             |
| 201   | AGACTAACTC CTCATAATCA ATTACCAGTG GCTGCTGCCA GTGGTGCTTT |       | CACCACGAAA  |
|       | TCTGATTGAG GAGATTTAGT TAATGGTCAC CGACGACGGT            |       |             |
| 251   | TGCATGTCTT TCCGGGTTGG ACTCAAGACG ATAGTTACCG GATAAGCGC  |       | CTATTCCGCG  |
|       | ACGTACAGAA AGGCCCCAACC TGAGTCTGC TATCAATGGC            |       |             |
| 301   | AGCGGTCGGA CTGAACGGGG GGTTCGTGCA TACAGTCCAG CTTGAGCGA  |       | GAACCTCGCT  |
|       | TCGCCAGCCT GACTTGCCCC CCAAGCACGT ATGTCAGGTC            |       |             |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```

351  ACTGCCCTACC CGGAAC TGTCAGGCGT GGAATGAGAC AAACGGCGCC
      TGACGGATGG GCCTTGACTC ACAGTCCGCA CCTTACTCTG TTTGCCGCCGG

      AgeI
      ~~~~~
401  ATAACAGCGG AATGACACCG GTAAACCGAA AGCAGGAAC AGGAGAGCGC
      TATTGTGCGC TTA CTGTGGC CATTTGGCTT TCCGTCCCTG TCCTCTCGCG

451  AGGAGGGAGC CGCCAGGGGG AAACGCCCTGG TATCTTTATA GTCTGTCTCG
      TCCTCCCTCG CGGTCCCCC TTTGCCGGACC ATAGAAATAT CAGGACAGCC

501  GTTTCGCCAC CACTGATTG AGCGTCAGAT TTCGTGATGC TTGTCAGGGG
      CAAAGCGGTG GTGACTAAAC TCGCAGTCTA AAGCACTACG AACAGTCCCC

551  GCGGGAGCCT ATGGAAAAAC GGCTTTGCCG CGGCCCTCTC ACTTCCCTGT
      CCGCCTCGGA TACCTTTTG CCGAAACGGC GCCGGGAGAG TGAAGGGACA

601  TAAGTATCTT CCTGGCATCT TCCAGGAAAT CTCCGCCCCCG TTCGTAAGCC
      ATTCATAGAA GGACCGTAGA AGTCCTTTA GAGCGGGGC AAGCATTCGG

651  ATTTCGGCTC GCCGCAGTCG AACGACCGAG CGTAGCGAGT CAGTGAGCGA
      TAAAGGCGAG CGGCGTCAGC TTGCTGGCTC GCATCGCTCA GTCACTCGCT

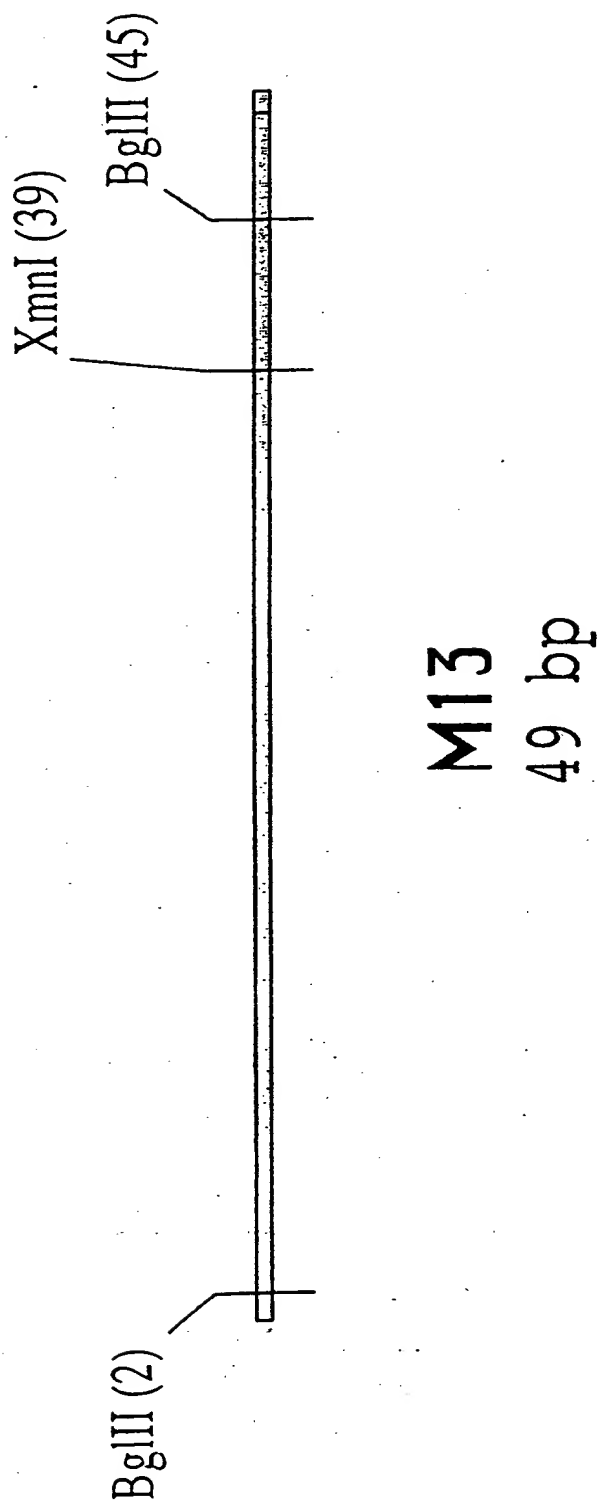
```

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |                                                                                                                    | AgeI  |
|-----|--------------------------------------------------------------------------------------------------------------------|-------|
| 701 | GGAAGCGGAA TATATCCTGT ATCACATATT CTGCTGACGC ACCGGTGCAG<br>CCTTCGCCCTT ATATAGGACA TAGTGTATAA GACGACTGCG TGGCCACGTC  | ~~~~~ |
|     |                                                                                                                    |       |
|     |                                                                                                                    | XmnI  |
|     |                                                                                                                    | ~~~~~ |
| 751 | CCTTTTCTTCT CCTGCCACAT GAAGCACTTC ACTGACACCC TCATCAGTGC<br>GGAAAAAAGA GGACGGTGTA CTTCGTGAAG TGA CTGTGGG AGTAGTCACG |       |
|     |                                                                                                                    |       |
|     |                                                                                                                    | NheI  |
|     |                                                                                                                    | ~~~~~ |
| 801 | CAACATAGTA AGCCAGTATA CACTCCGCTA GC<br>GTTGTATCAT TCGGTCATAT GTGAGGCGAT CG                                         |       |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



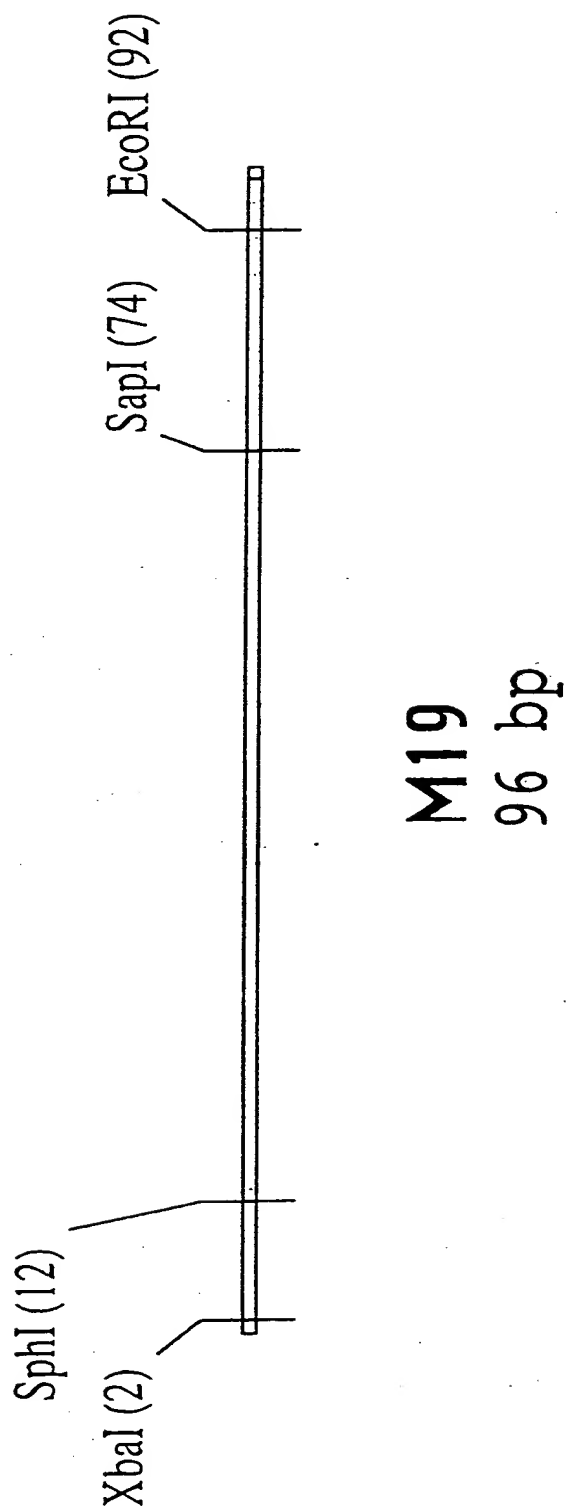
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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 13:

|   | BglII      | XmnI       | BglII      |
|---|------------|------------|------------|
|   | ~~~~~      | ~~~~~      | ~~~~~      |
| 1 | AGATCTCATA | ACTTCGTATA | ATGTATGCTA |
|   | TCTAGAGTAT | TGAAGCATAT | TACATACGAT |
|   |            |            | ATGCTTCAAT |
|   |            |            | AAGTCTAGA  |
|   |            |            | TTCAGATCT  |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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**M 19:**

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

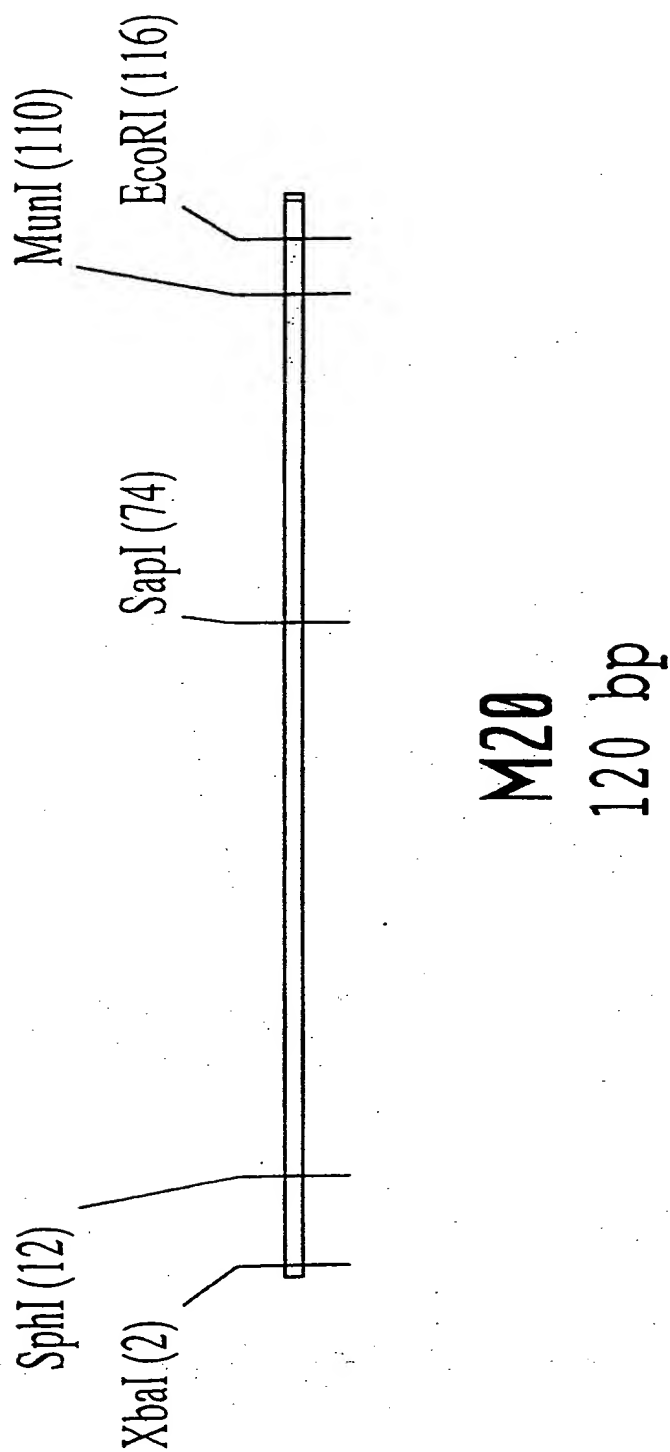


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 20:

|     | XbaI        | SphI       |                                  |
|-----|-------------|------------|----------------------------------|
| 1   | TCTAGAGCAT  | GCGTAGGAGA | AAATAAAATG AAACAAGCA CTATTGCACT  |
|     | AGATCTCGTA  | CGCATCCTCT | TTTATTTTAC TTTGTTTCGT GATAACGTGA |
|     |             |            |                                  |
|     |             | SapI       |                                  |
|     |             | -----      |                                  |
| 51  | GGCACTCTTA  | CCGTTGCTCT | TCACCCCTGT TACCAAAGCC GACTACAAAG |
|     | CCGTGAGAAAT | GGCAACGAGA | AGTGGGGACA ATGGTTTCGG CTGATGTTTC |
|     |             |            |                                  |
|     | MunI        | EcoRI      |                                  |
|     | -----       | -----      |                                  |
| 101 | ATGAAGTGCA  | ATTGGAATTC |                                  |
|     | TACTTCACGT  | TAACCTTAAG |                                  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

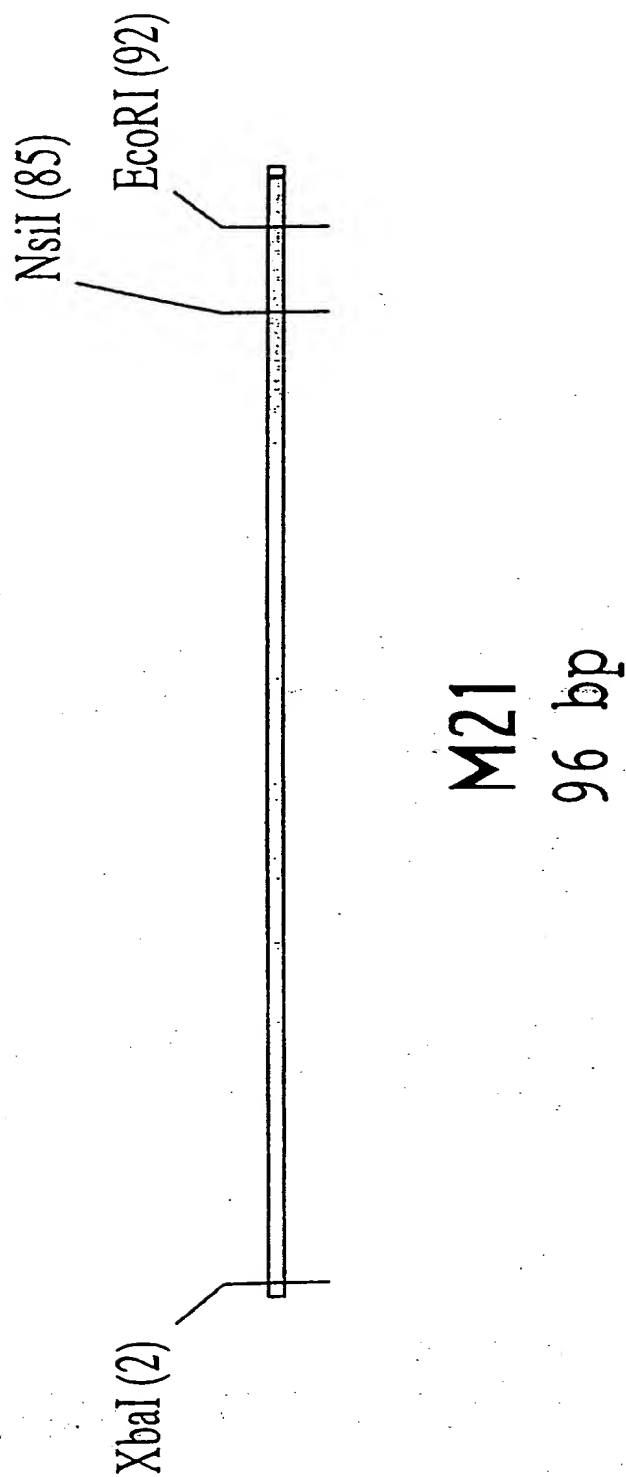


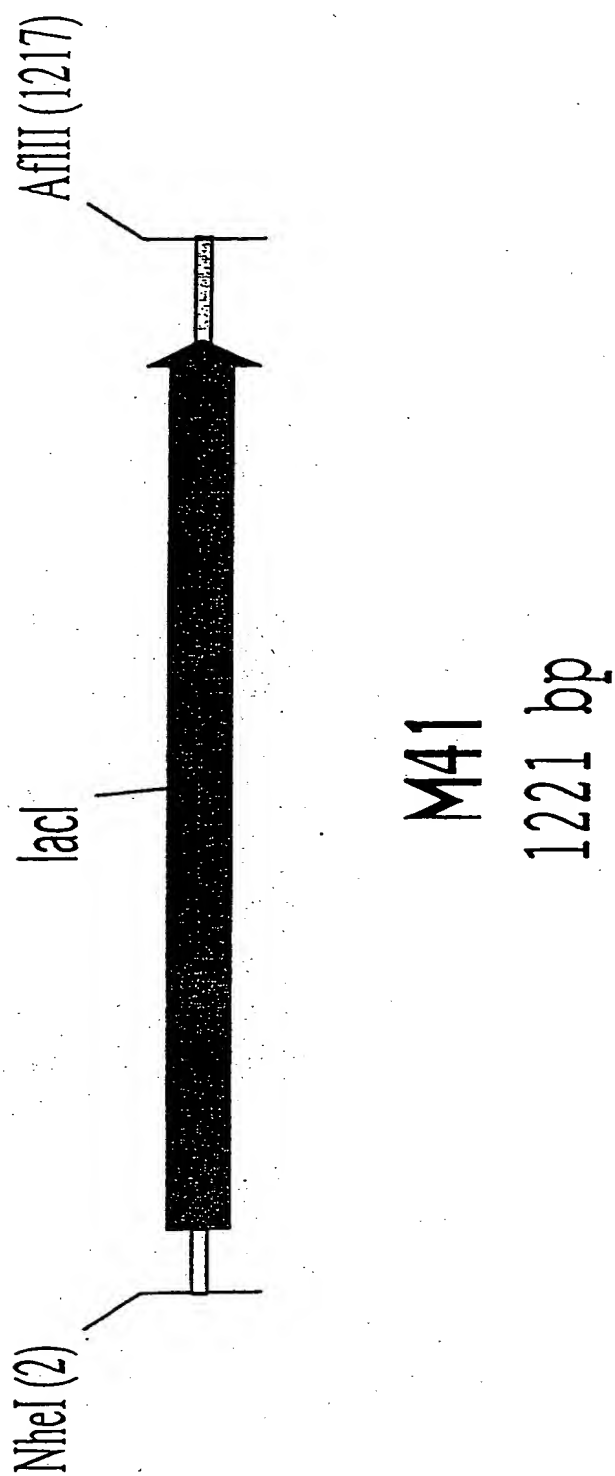
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 21:

|    |                                                       |       |       |  |
|----|-------------------------------------------------------|-------|-------|--|
|    | XbaI                                                  |       |       |  |
|    | ~~~~~                                                 |       |       |  |
| 1  | TCTAGAGGTT GAGGTGATT TATGAAAAG AATATCGCAT TTCTTCTTGC  |       |       |  |
|    | AGATCTCCAA CTCCACTAAA ATACTTTTC TTATAGCGTA AAGAAGAACG |       |       |  |
|    |                                                       | NsiI  | ECORI |  |
|    |                                                       | ~~~~~ | ~~~~~ |  |
| 51 | ATCTATGTC GTTTTCTA TTGCTACAA TGCATACGCT GAATTC        |       |       |  |
|    | TAGATACAAG CAAAAAGAT AACGATGTT ACGTATGCCA CTTAAG      |       |       |  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

M 41:

```

      NheI
      ---
1  GCTAGCATQG AATGGCGCAA AACCTTTCGC GGTATGGCAT GATAGCGCCC
   CGATCGTAGC TTACCGCGTT TTGGAAAGCG CCATACCGTA CTATCGCGGG

51  GAAGAGAGT CAATTCAGGG TGGTGAATGT GAAACCAGTA ACGTTATACG
   CCTTCTCTCA GTTAAGTCCC ACCACTTACA CTTTGGTCAT TGCAATATGC

101 ATGTCGCAGA GTATGCCGGT GTCTCTTATC AGACCGTTTC CCGCGTGGTG
   TACAGCGTCT CATACGGCCA CAGAGAATAG TCTGGCAAAG GGCGCACCCAC

151 AACCAGGCCA GCCACGTTTC TGCGAAACG CGGGAAAAAG TGGAAGCGGC
   TTGGTCCGGT CCGTGCAAAG ACGCTTTTGC GCCCTTTTTC ACCTTCGCCG

201 GATGGCGGAG CTGAATTACA TTCCTAACCG CGTGGCACAA CAACTGGCGG
   CTACCGCCTC GACTTAATGT AAGGATTGGC GCACCGTGTT GTTGACCGCC

251 GCAAACAGTC GTTGCTGATT GGCGTTGCCA CCTCCAGTCT GGCCCTGCAC
   CGTTTGTGTCAG CAACGACTAA CCGCAACGGT GGAGGTCAGA CCGGGACGTG

301 GCGCCGTCGC AAATTGTCGC GGCGATTAAA TCTCGCGCCG ATCAACTGGG
   CGCGGCAGCG TTTAACAGCG CCGCTAATTT AGAGCGCGGC TAGTTGACCC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |            |             |            |            |             |
|-----|------------|-------------|------------|------------|-------------|
| 351 | TGCCAGCGTG | GTCGTGTCGA  | TGGTAGAACG | AAGCGGCGTC | GAAGCCTGTA  |
|     | ACGGTCGCAC | CAGCACAGCT  | ACCATCTTGC | TTCGCCGCAG | CTTCGGACAT  |
| 401 | AAGCGGCGGT | GCACAATCTT  | CTCGGCAAC  | GTGTCAGTGG | GCTGATTATT  |
|     | TTCGCCGCCA | CGTGTTAGAA  | GAGCGCGTTG | CACAGTCACC | CGACTAATAA  |
| 451 | AACTATCCGC | TGGATGACCA  | GGATGCTATT | GCTGTGGAAG | CTGCCCTGCAC |
|     | TTGATAGGCG | ACCTACTGGT  | CCTACGATAA | CGACACCTTC | GACGGACGTG  |
| 501 | TAATGTTCCG | GCGTTATTTC  | TTGATGTCTC | TGACCAGACA | CCCATCAACA  |
|     | ATTACAAGGC | CGCAATAAAG  | AACTACAGAG | ACTGGTCTGT | GGTAGTTGT   |
| 551 | GTATTATTTT | CTCCCATGAG  | GACGGTACGC | GACTGGGCGT | GGAGCATCTG  |
|     | CATAATAAAA | GAGGGTACTC  | CTGCCATGCG | CTGACCCGCA | CCTCGTAGAC  |
| 601 | GTCGCATTGG | GCCACCAGCA  | AATCGCGCTG | TTAGCTGGCC | CATTAAAGTTC |
|     | CAGCGTAACC | CGGTGGTTCGT | TTAGCGCGAC | AATCGACCGG | GTAATTCAAG  |
| 651 | TGTCTCGGCG | CGTCTGCGTC  | TGGCTGGCTG | GCATAAATAT | CTCACTCGCA  |
|     | ACAGAGCCGC | GCAGACGCAG  | ACCGACCGAC | CGTATTTATA | GAGTGAGCGT  |
| 701 | ATCAAATTCA | GCCGATAGCG  | GAACGGGAAG | GCGACTGGAG | TGCCATGTCC  |
|     | TAGTTTAAGT | CGGCTATCGC  | CTTGCCCTTC | CGCTGACCTC | ACGGTACAGG  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |            |             |             |             |             |
|------|------------|-------------|-------------|-------------|-------------|
| 751  | GGTTTCAAC  | AAACCATGCA  | AATGCTGAAT  | GAGGCAATCG  | TTCCCCACTGC |
|      | CCAAAAGTTG | TTTGGTACGT  | TTACGACTTA  | CTCCCGTAGC  | AAGGGTGACG  |
| 801  | GATGCTGGTT | GCCAACGATC  | AGATGGCGCT  | GGCGGCAATG  | CGTGCCATTA  |
|      | CTACGACCAA | CGGTGCTAG   | TCTACCGCGA  | CCCGCGTTAC  | GCACGGTAAT  |
| 851  | CCGAGTCCGG | GCTGCGCGTT  | GGTGCGGACA  | TCTCGGTAGT  | GGGATACGAC  |
|      | GGCTCAGGCC | CGACGCGCAA  | CCACGCCCTGT | AGAGCCATCA  | CCCTATGCTG  |
| 901  | GATACCGAGG | ACAGCTCATG  | TTATATCCCG  | CCGCTGACCA  | CCATCAAACA  |
|      | CTATGGCTCC | TGTCGAGTAC  | AAATATAGGC  | GCGACTGGT   | GGTAGTTGT   |
| 951  | GGATTTTCGC | CTGCTGGGGC  | AAACCAGCGT  | GGACCGCTTG  | CTGCCAACTCT |
|      | CCTAAAAGCG | GACGACCCCG  | TTTGGTCGCA  | CCTGGCGAAC  | GACGTTGAGA  |
| 1001 | CTCAGGGCCA | GGCGGTGAAG  | GGCAATCAGC  | TGTTGCCCCGT | CTCACTGGTG  |
|      | GAGTCCCGGT | CCGCCACTTC  | CCGTTAGTCG  | ACAAACGGCA  | GAGTGACCAC  |
| 1051 | AAAAGAAAAA | CCACCCCTGGC | TCCCAATACG  | CAAACCGCCT  | CTCCCCGCGC  |
|      | TTTTCTTTTT | GGTGGGACCG  | AGGTTATGC   | GTTTGGCGGA  | GAGGGGCGCG  |
| 1101 | GTTGGCCGAT | TCACTGATGC  | AGCTGGCACG  | ACAGGTTTCC  | CGACTGGAAA  |
|      | CAACCGGCTA | AGTGACTACG  | TCGACCGTGC  | TGTCCAAAGG  | GCTGACCTTT  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

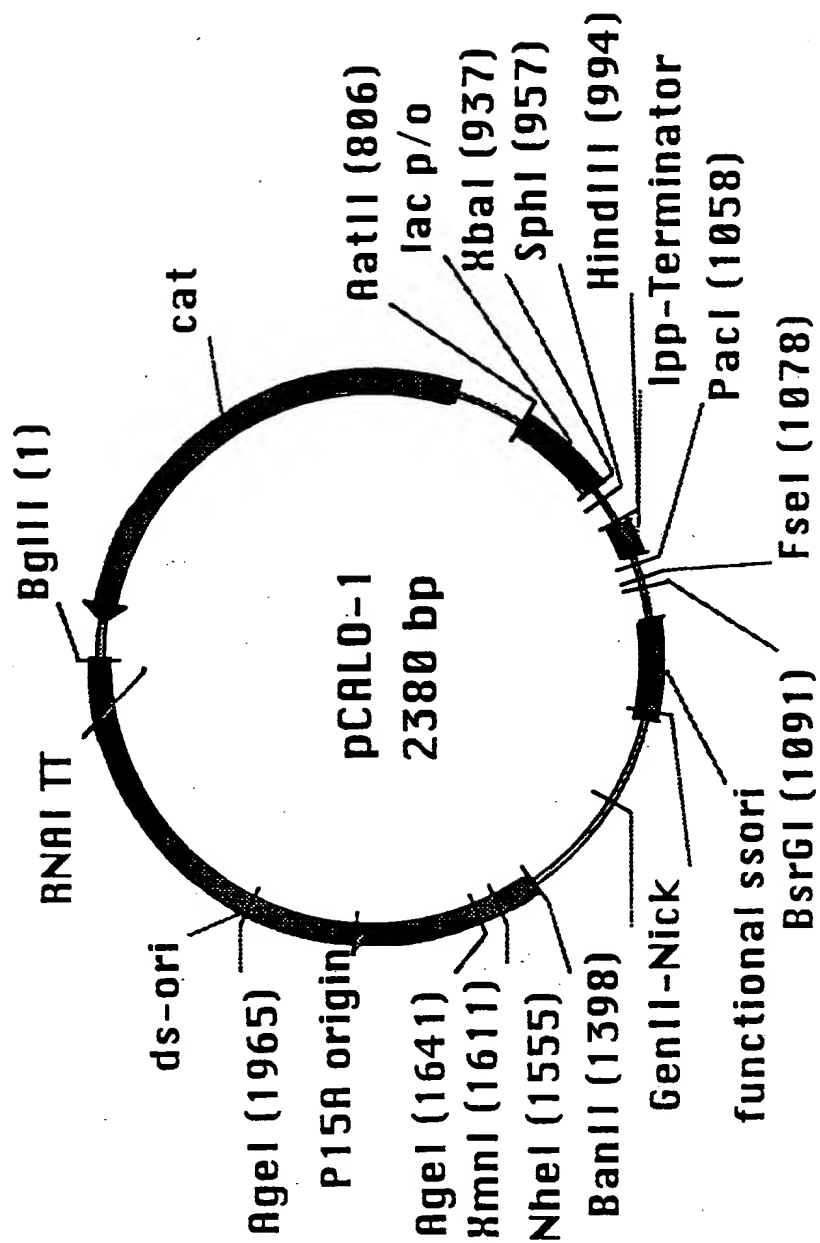
1151 GCGGGCAGTG AGGCTACCCG ATAAAAGCGG CTTCCCTGACA GGAGGCCCGTT  
CGCCCGTCAC TCCGATGGC TATTTCGCC GAAGGACTGT CCTCCGGCAA

AflII

-----

1201 TTGTTTGTCA GCCCACTTAA G  
AACAAAACGT CGGTGAATT C

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

pCALO-1:  
 BglII  
 ~~~~~

|     |            |             |            |             |             |
|-----|------------|-------------|------------|-------------|-------------|
| 1   | GATCTAGCAC | CAGGCGTTTA  | AGGGCACCAA | TAACTGCCCTT | AAAAAAATTA  |
|     | CTAGATCGTG | GTCCGCAAAAT | TCCCGTGTTT | ATTGACGGAA  | TTTTTTTAAAT |
| 51  | CGCCCCGCC  | TGCCACTCAT  | CGCAGTACTG | TTGTAATTCA  | TTAAGCATTC  |
|     | GCGGGCGGG  | ACGGTGAGTA  | GCGTCATGAC | AACATTAAAGT | AATTCGTAAG  |
| 101 | TGCCGACATG | GAAGCCATCA  | CAAACGGCAT | GATGAACCTG  | AATCGCCAGC  |
|     | ACGGCTGTAC | CTTCGGTAGT  | GTTTGCCGTA | CTACTTGGAC  | TTAGCGGTCTG |
| 151 | GGCATCAGCA | CCTTGTCGCC  | TTGCGTATAA | TATTTGCCCA  | TAGTGAAAAC  |
|     | CCGTAGTCGT | GGAACAGCGG  | AACGCATATT | ATAAACGGGT  | ATCACTTTTG  |
| 201 | GGGGCGGAAG | AAGTTGTCCA  | TATTGGCTAC | GTTTAAATCA  | AAACTGGTGA  |
|     | CCCCCGCTTC | TTCAACAGGT  | ATAACCGATG | CAAATTTAGT  | TTTGACCCACT |
| 251 | AACTCACCCA | GGGATTGGCT  | GAGACGAAA  | ACATATCTC   | AATAAACCCCT |
|     | TTGAGTGGGT | CCCTAACCGA  | CTCTGCTTTT | TGTATAAGAG  | TTATTTGGGA  |
| 301 | TTAGGGAAAT | AGGCCAGGTT  | TTCACCGTAA | CACGCCACAT  | CTTGCGAATA  |
|     | AATCCCTTTA | TCCGGTCCAA  | AAGTGGCATT | GTGCGGTGTA  | GAACGCTTAT  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```

351  TATGTGTAGA AACTGCCGGA AATCGTCGTG GTATTCACTC CAGAGCGATG
    ATACACATCT TTGACGGCCT TTAGCAGCAC CATAAGTGAG GTCTCGCTAC

401  AAAACGTTTC AGTTTGCTCA TGGAAAACGG TGTAACAAGG GTGAACACTA
    TTTTGCAAAG TCAAACGAGT ACCTTTTGCC ACATTGTTCC CACTTGTGAT

451  TCCCATATCA CCAGCTCACC GTCTTTCATT GCCATACGGA ACTCCGGGTG
    AGGTATAGT GGTGAGTGG CAGAAAGTAA CGGTATGCCT TGAGGCCCCAC

501  AGCATTCATC AGCGGGGCAA GAATGTGAAT AAAGGCCGGA TAAAACTTGT
    TCGTAAAGTAG TCCGCCCGGT CTTACACTTA TTTCGGCCTT ATTTTGAACA

551  GCTTATTTTT CTTTACGGTC TTTAAAAAGG CCGTAATATC CAGCTGAACG
    CGAATAAAAA GAAATGCCAG AAATTTTCC GCATTATAG GTCGACTTGC

601  GTCTGGTTAT AGGTACATTG AGCAACTGAC TGAAATGCCCT CAAATGTTT
    CAGACCAATA TCCATGTAAC TCGTTGACTG ACTTTACGGA GTTTTACAAG

651  TTTACGATGC CATTGGGATA TATCAACGGT GGTATATCCA GTGATTTTTT
    AAATGCTACG GTAACCCCTAT ATAGTTGCCA CCATATAGGT CACTAAAAAA

701  TCTCCATTTT AGCTTCCTTA GCTCCTGAAA ATCTCGATAA CTCAAAAAAT
    AGAGGTAAAA TCGAAGGAAT CGAGGACTTT TAGAGCTATT GAGTTTTTAA

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```

751  ACGCCCGGTA GTGATCTTAT TTCAATTATGG TGAAAGTTGG AACCTCACCC
    TCGGGGCCAT CACTAGAATA AAGTAATACC ACTTTCAACC TTGGAGTGGG

    AatII
    ~~~~~
801  GACGTCTAAT GTGAGTTAGC TCACTCATTA GGCACCCCCAG GCTTTACACT
    CTGCAGATTA CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA

851  TTATGCTTCC GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT
    AATACGAAGG CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA

                                XbaI
                                ~~~~~
901  CACACAGGAA ACAGCTATGA CCATGATTAC GAATTTCTAG ACCCCCCCCC
    GTGTGTCCTT TGTCGATACT GGTACTAATG CTTAAAGATC TGGGGGGGGG

                                SphI
                                ~~~~~
951  CGCATGCCAT AACTTCGTAT AATGTACGCT ATACGAAGTT ATAAGCTTGA
    GCGTACGGTA TTGAAGCATA TTACATGCCA TATGCTTCAA TATTCGAAC

                                HindIII
                                ~~~~~
1001 CCTGTGAAGT GAAAATGGC GCAGATTGTG CGACATTTT TTTGTCTGCC
    GGACACTTCA CTTTTTACCG CGCTAACAC GCTGTAAAAA AACAGACGG
  
```

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      | PacI  | FseI  | BsrGI |
|------|---|-------|-------|
|      | ~~~~~   | ~~~~~ | ~~~~~ |
| 1051 | GTTTAATTAA AGGGGGGGG GGGCGGCCCT GGGGGGGGT GTACATGAAA<br>CAAATTAAAT TCCCCCCCCC CCGGCCGGA CCCCCCCCCA CATGTACTTT     |       |       |
| 1101 | TTGTAAACGT TAATATTTG TTAATAATTCG CGTTAAATTT TTGTTAAATC<br>AACATTTGCA ATTATAAAAC AATTTAAGC GCAATTTAAA AACAAATTAG   |       |       |
| 1151 | AGCTCATTTT TTAACCAATA GGCCGAAATC GGCAAAATCC CTTATAAATC<br>TCGAGTAAAA AATTGGTTAT CCGGCTTAG CCGTTTAGG GAATATTAG     |       |       |
| 1201 | AAAAGAATAG ACCGAGATAG GGTGAGTGT TGTCCAGTT TGGAAACAAGA<br>TTTCTCTATC TGGCTCTATC CCAACTCACA ACAAGGTCAA ACCTTGTTCT   |       |       |
| 1251 | GTCCACTATT AAAGAACGTG GACTCCAACG TCAAAGGGCG AAAAACCGTC<br>CAGGTGATAA TTTCTTGCAC CTGAGGTTGC AGTTTCCCGC TTTTGGGCAG  |       |       |
| 1301 | TATCAGGGCG ATGGCCCACT ACGAGAACCA TCACCCCTAAT CAAGTTTTTT<br>ATAGTCCCGC TACCGGGTGA TGCTCTTGGT AGTGGGATTA GTTCAAAAAA |       |       |
|      |   |       | BanII |
|      |   |       | ~~~~~ |
| 1351 | GGGTCGAGG TGCCGTAAG CACTAAATCG GAACCCCTAAA GGGAGCCCCC<br>CCCCAGCTCC ACGGCATTTC GTGATTTAGC CTTGGGATTT CCTCGGGGG    |       |       |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|               |  |
|---------------|--|
| 1401          | GATTAGAGC TTGACGGGA AAGCCGGCGA ACGTGGCGAG AAAGGAAGGG<br>CTAAATCTCG AACTGCCCTT TTCGGCCGCT TGCACCGCTC TTTCCTTCCC   |
| 1451          | AAGAAAGCGA AAGAGCGGG CGCTAGGGCG CTGGCAAGTG TAGCGGTCAC<br>TTCTTTTCGCT TTCTCTCGCC GCGATCCCGC GACCGTTTAC ATCGCCAGTG |
| 1501          | GCTGCGCGTA ACCACCACAC CCGCCGCGCT TAATGCGCCG CTACAGGGCG<br>CGACGCGCAT TGGTGGTGTG GCGGCGCGCA ATTACGCGGC GATGTCCCGC |
| NheI<br>~~~~~ |  |
| 1551          | CGTGCTAGCG GAGTGATAC TGGCTTACTA TGTTGGCACT GATGAGGGTG<br>GCACGATCGC CTCACATATG ACCGAATGAT ACAACCGTGA CTAATCCCCAC |
| XmnI<br>~~~~~ |  |
| 1601          | TCAGTGAAGT GCTTCATGTG GCAGGAGAAA AAAGGCTGCA CCGGTGCGTC<br>AGTCACTTCA CGAAGTACAC CGTCTCTTTT TTTCGACGT GGCCACGCAG  |
| 1651          | AGCAGAATAT GTGATACAGG ATATATTCCG CTTCCTCGCT CACTGACTCG<br>TCGTCTTATA CACTATGTCC TATATAAGGC GAAGGAGCGA GTGACTGAGC |
| 1701          | CTACGCTCGG TCGTTCGACT GCGGCGAGCG GAAATGGCTT ACGAACGGGG   |

AgeI  
~~~~~

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |            |            |            |             |
|------|-------------|------------|------------|------------|-------------|
|      | GATGCGAGCC  | AGCAAGCTGA | CGCCGCTCGC | CTTTACCGAA | TGCTTGCCCC  |
| 1751 | CGGAGATTTC  | CTGGAAGATG | CCAGGAAGAT | ACTTAACAGG | GAAAGTGAGAG |
|      | GCCTCTAAAG  | GACCTTCTAC | GGTCCTTCTA | TGAATTGTCC | CTTCACTCTC  |
| 1801 | GGCCGCGGCA  | AAGCCGTTTT | TCCATAGGCT | CCGCCCCCT  | GACAAGCATC  |
|      | CCGGCGCCGT  | TTCGGCAAAA | AGTATCCGA  | GGCGGGGGA  | CTGTTCTGTAG |
| 1851 | ACGAAATCTG  | ACGCTCAAAT | CAGTGGTGGC | GAAACCCGAC | AGGACTATAA  |
|      | TGCTTTTAGAC | TGCGAGTTTA | GTCACCACCG | CTTTGGGCTG | TCCTGATATT  |
| 1901 | AGATACCAGG  | CGTTTCCCCC | TGGCGGCTCC | CTCCTGCGCT | CTCCTGTTCC  |
|      | TCTATGGTCC  | GCAAAGGGG  | ACCGCCGAGG | GAGGACGCCA | GAGGACAAGG  |
|      |             | AgeI       | ~~~~~      |            |             |
| 1951 | TGCCCTTTCGG | TTTACCGGTG | TCATTCCGCT | GTTATGGCCG | CGTTTGTCTC  |
|      | ACGGAAAGCC  | AAATGGCCAC | AGTAAGGCCA | CAATACCCGC | GCAAACAGAG  |
| 2001 | ATTCCACGCC  | TGACACTCAG | TTCCGGGTAG | GCAGTTCGCT | CCAAGCTGGA  |
|      | TAAGGTGCCG  | ACTGTAGTC  | AAGGCCCATC | CGTCAAGCGA | GGTTCGACCT  |
| 2051 | CTGTATGCAC  | GAACCCCCCG | TTCAGTCCGA | CCGCTGCGCC | TTATCCGGTA  |
|      | GACATACGTG  | CTTGGGGGGC | AAGTCAGGCT | GGCGACGCCG | AATAGGCCAT  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|       |            |            |            |             |             |
|-------|------------|------------|------------|-------------|-------------|
| 2101  | ACTATCGTCT | TGAGTCCAAC | CCGGAAGAC  | ATGCAAAAGC  | ACCACTGGCA  |
|       | TGATAGCAGA | ACTCAGGTTG | GGCCTTTCTG | TACGTTTTCG  | TGGTGACCGT  |
| 2151  | GCAGCCACTG | GTAATTGATT | TAGAGGAGTT | AGTCTTGAAG  | TCATGCGCCG  |
|       | CGTCGGTGAC | CATTAACTAA | ATCTCCTCAA | TCAGAACTTC  | AGTACGCGGC  |
| 2201  | GTTAAGGCTA | AACTGAAAGG | ACAAGTTTTA | GTGACTGCGC  | TCCCTCCAAGC |
|       | CAATTCCGAT | TTGACTTTCC | TGTTCAAAAT | CACTGACGCG  | AGGAGGTTCC  |
| 2251  | CAGTTACCTC | GGTTCAAAGA | GTTGGTAGCT | CAGAGAACCCT | ACGAAAACC   |
|       | GTCAATGGAG | CCAAGTTTCT | CAACCATCGA | GTCTCTTGG   | TGCTTTTGG   |
| 2301  | GCCCTGCAAG | GCGGTTTTTT | CGTTTTCAGA | GCAAGAGATT  | ACGCGCAGAC  |
|       | CGGGACGTC  | CGCCAAAAAA | GCAAAAGTCT | CGTCTCTAA   | TGCGCGTCTG  |
| BglII |            |            |            |             |             |
| 2351  | CAAACGATC  | TCAAGAAGAT | CATCTTATTA |             |             |
|       | GTTTGCTAG  | AGTTCTTCTA | GTAGAATAAT |             |             |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

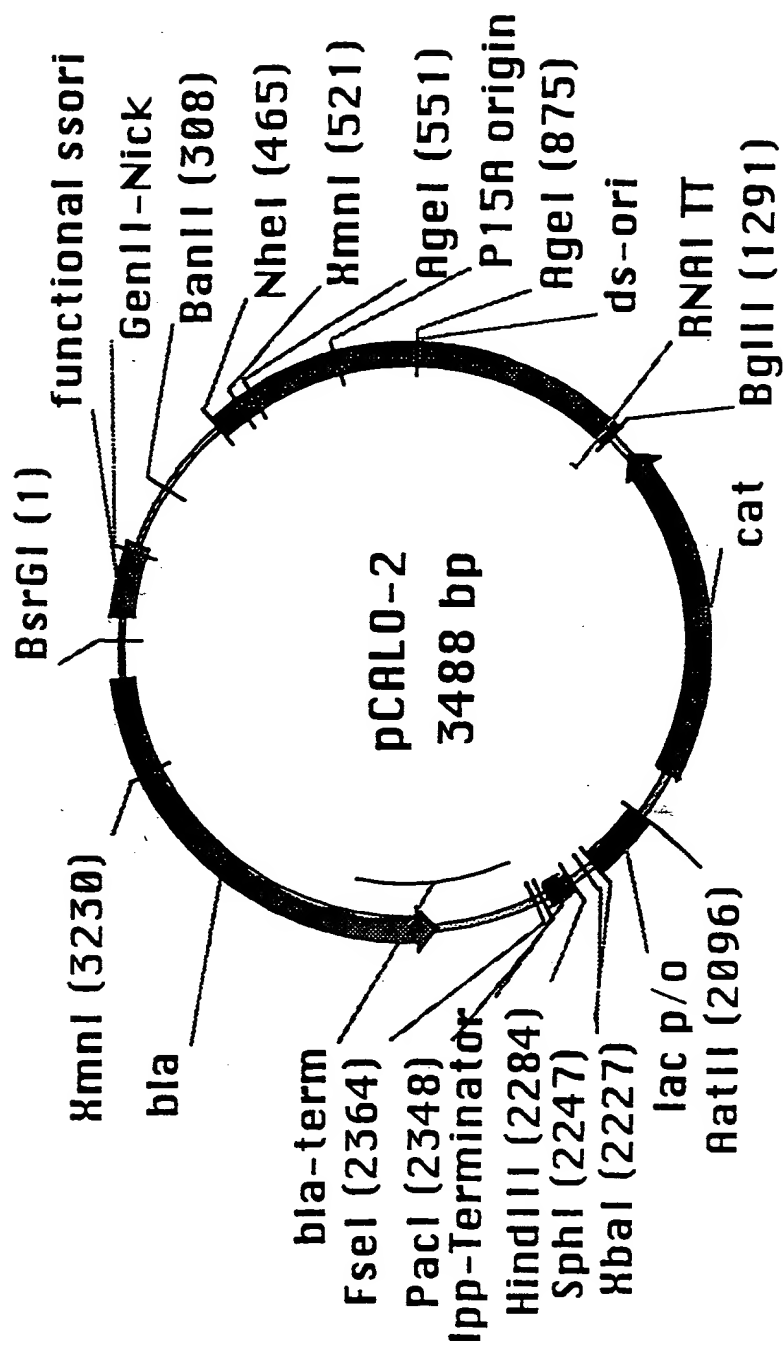




Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|          |             |             |            |             |             |
|----------|-------------|-------------|------------|-------------|-------------|
| pCALO-2: |             |             |            |             |             |
| BsrGI    |             |             |            |             |             |
| ~~~~~    |             |             |            |             |             |
| 1        | GTACATGAAA  | TTGTAAACGT  | TAATATTTTG | TTAAAAATTCG | CGTTAAATTT  |
|          | CATGTACTTT  | AACATTTGCA  | ATTATAAAAC | AATTTAAGC   | GCAATTTAAA  |
| 51       | TTGTTAAATC  | AGCTCATTTT  | TTAACCAATA | GGCCGAAATC  | GGCAAAATCC  |
|          | AACAATTAG   | TCGAGTAAAA  | AATTGGTTAT | CCGGCTTAG   | CCGTTTTAGG  |
| 101      | CTTATAAATC  | AAAAGAAATAG | ACCGAGATAG | GGTTGAGTGT  | TGTTCCAGTT  |
|          | GAATATTAG   | TTTTTCTTATC | TGGCTCTATC | CCAACTCACA  | ACAAGGTCAA  |
| 151      | TGGAACAAGA  | GTCCACTATT  | AAAGAACGTG | GACTCCAACG  | TCAAAGGGCG  |
|          | ACCTTGTTCT  | CAGGTGATAA  | TTTCTTGAC  | CTGAGGTTGC  | AGTTTCCCGC  |
| 201      | AAAAACCGTC  | TATCAGGGCG  | ATGGCCCACT | ACGAGAACCA  | TCACCCCTAAT |
|          | TTTTTTGGCAG | ATAGTCCCGC  | TACCGGGTGA | TGCTCTTGGT  | AGTGGGATTA  |
| 251      | CAAGTTTTTT  | GGGTCGAGG   | TGCCGTAAAG | CAC TAAATCG | GAACCC TAAA |
|          | GTTCAAAAAA  | CCCCAGCTCC  | ACGGCATTTT | GTGATTTAGC  | CTTGGGATTT  |
| BanII    |             |             |            |             |             |
| ~~~~~    |             |             |            |             |             |
| 301      | GGGAGCCCCC  | GATTTAGAGC  | TTGACGGGGA | AAGCCGGCGA  | ACGTGGCGAG  |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |            |             |             |            |            |
|-----|------------|-------------|-------------|------------|------------|
|     | CCCTCGGGG  | CTAAATCTCG  | AACTGCCCCCT | TTCGGCCGCT | TGCACCGCTC |
| 351 | AAAGGAAGG  | AAGAAAGCGA  | AAGGAGCGGG  | CGCTAGGGCG | CTGGCAAGTG |
|     | TTTCCTTCCC | TTCTTTTCGCT | TTCCTCGCCC  | GCGATCCCCG | GACCGTTCAC |
| 401 | TAGCGGTCAC | GCTGCCGGTA  | ACCACCACAC  | CCGCCGCGCT | TAATGCGCCG |
|     | ATCGCCAGTG | CGACGCGCAT  | TGGTGGTGTG  | GGCGCGCGGA | ATTACGCGGC |
|     | NheI       |             |             |            |            |
|     | ~~~~~      |             |             |            |            |
| 451 | CTACAGGCG  | CGTGCTAGCG  | GAGTGATAC   | TGGCTTACTA | TGTTGGCACT |
|     | GATGTCCCG  | GCACGATCGC  | CTCACATATG  | ACCGAATGAT | ACAACCGTGA |
|     | AgeI       |             |             |            |            |
|     | ~~~~~      |             |             |            |            |
|     | XmnI       |             |             |            |            |
|     | ~~~~~      |             |             |            |            |
| 501 | GATGAGGGTG | TCAGTGAAGT  | GCTTCATGTG  | GCAGGAGAAA | AAAGGCTGCA |
|     | CTACTCCAC  | AGTCACTTCA  | CGAAGTACAC  | CGTCCCTCTT | TTTCCGACGT |
|     | AgeI       |             |             |            |            |
|     | ~~~~~      |             |             |            |            |
| 551 | CCGTGCGTC  | AGCAGAAATAT | GTGATACAGG  | ATATATTCCG | CTTCCTCGCT |
|     | GGCCACGCAG | TCGTCTTATA  | CACTATGTCC  | TATATAAGGC | GAAGGAGCGA |
| 601 | CACTGACTCG | CTACGCTCGG  | TCGTTGCACT  | GCGGCGAGCG | GAAATGGCTT |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |            |            |            |            |             |
|-----|------------|------------|------------|------------|-------------|
|     | GTGACTGAGC | GATCGAGCC  | AGCAAGCTGA | CGCCGCTCGC | CTTTACCGAA  |
| 651 | ACGAACGGGG | CGGAGATTTC | CTGGAAGATG | CCAGGAAGAT | ACTTAACAGG  |
|     | TGCTTGCCCC | GCCTCTAAAG | GACCTTCTAC | GGTCCTTCTA | TGAATTGTCC  |
| 701 | GAAGTGAGAG | GGCCGCGGCA | AAGCCGTTTT | TCCATAGGCT | CCGCCCCCCT  |
|     | CTTCACTCTC | CCGGCGCCGT | TTCGGCAAAA | AGGTATCCGA | GGCGGGGGA   |
| 751 | GACAAGCATC | ACGAAATCTG | ACGCTCAAAT | CAGTGGTGGC | GAAACCCCGAC |
|     | CTGTTCGTAG | TGCTTTAGAC | TGCGAGTTTA | GTCACCAACG | CTTTGGGCTG  |
| 801 | AGGACTATAA | AGATACCAGG | CGTTTCCCCC | TGGCGGCTCC | CTCCTGCGCT  |
|     | TCCTGATATT | TCTATGGTCC | GCAAAGGGGG | ACCGCCGAGG | GAGGACGCCA  |
|     |            |            | AgeI       |            |             |
|     |            |            | ~~~~~      |            |             |
| 851 | CTCCTGTTCC | TGCCTTTCGG | TTTACCGGTG | TCATTCCGCT | GTTATGGCCG  |
|     | GAGGACAAGG | ACGGAAAGCC | AAATGGCCAC | AGTAAGGCCA | CAATACCCGC  |
| 901 | CGTTTGTCCT | ATTCCACGCC | TGACACTCAG | TTCCGGGTAG | GCAGTTCGCT  |
|     | GCAAACACAG | TAAGGTGCGG | ACTGTAGTC  | AAGGCCCATC | CGTCAAGCCA  |
| 951 | CCAAGCTGGA | CTGTATGCAC | GAACCCCCCG | TTCAGTCCGA | CCGCTGCGCC  |
|     | GGTTCGACCT | GACATACGTG | CTTGGGGGGC | AAGTCAGGCT | GGCGACGCCG  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |            |            |             |            |
|------|-------------|------------|------------|-------------|------------|
| 1001 | TTATCCGGTA  | ACTATCGTCT | TGAGTCCAAC | CCGGAAGAC   | ATGCAAAAGC |
|      | AATAGGCCAT  | TGATAGCAGA | ACTCAGGTG  | GGCCTTTCTG  | TACGTTTTCG |
| 1051 | ACCACTGGCA  | GCAGCCACTG | GTAATTGATT | TAGAGGAGTT  | AGTCTTGAAG |
|      | TGGTGACCGT  | CGTCGGTGAC | CATTAACTAA | ATCTCCTCAA  | TCAGAACTTC |
| 1101 | TCATGCGCCG  | GTTAAGGCTA | AACTGAAAGG | ACAAAGTTTA  | GTGACTGCGC |
|      | AGTACGCGGC  | CAATTCCGAT | TTGACTTTCC | TGTTCAAAAT  | CACTGACGCG |
| 1151 | TCCTCCAAGC  | CAGTTACCTC | GGTTCAAAGA | GTTGGTAGCT  | CAGAGAACCT |
|      | AGGAGGTTTCG | GTCAATGGAG | CCAAGTTTCT | CAACCATCGA  | GTCTCTTGGA |
| 1201 | ACGAAAAACC  | GCCCTGCAAG | GCGGTTTTTT | CGTTTTCAGA  | GCAAGAGATT |
|      | TGCTTTTTCG  | CGGGACGTTT | CGCCAAAAAA | GCAAAAGTCT  | CGTTCTCTAA |
|      |             |            |            | BglII       |            |
|      |             |            |            | ~~~~~       |            |
| 1251 | ACGCGCAGAC  | CAAAACGATC | TCAAGAAGAT | CATCTTATTA  | GATCTAGCAC |
|      | TGCGCGTCTG  | GTTTTGCTAG | AGTTCTTCTA | GTAGAATAAT  | CTAGATCGTG |
| 1301 | CAGGCGTTTA  | AGGCAACCAA | TAACTGCCTT | AAAAAATTA   | CGCCCCGCCC |
|      | GTCCGCAAAT  | TCCCGTGGTT | ATTGACGGAA | TTTTTTTAAAT | GCGGGGCGGG |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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1351  TGCCACTCAT  CGCAGTACTG  TTGTAATTCA  TTAAGCATTC  TGCCGACATG
      ACGGTGAGTA  GCGTCATGAC  AACATTAAAGT  AATTCGTAAG  ACGGCTGTAC

1401  GAAGCCATCA  CAAACGGCAT  GATGAACCTG  AATCGCCAGC  GGCATCAGCA
      CTTCGGTAGT  GTTTGCCGTA  CTACTTGGAC  TTAGCGGTCTG  CCGTAGTCGT

1451  CCTTGTCGCC  TTGCGTATAA  TATTTGCCCA  TAGTGAAAAC  GGGGGCGAAG
      GGAACAGCGG  AACGCATATT  ATAAACGGGT  ATCACTTTTG  CCCCCGCTTC

1501  AAGTTGTCCA  TATTGGCTAC  GTTAAATCA  AAACCTGGTGA  AACTCACCCA
      TTCAACACAGT  ATAACCGATG  CAAATTAGT  TTGACCCACT  TTGAGTGGGT

1551  GGGATTGGCT  GAGACGAAAA  ACATATTCTC  AATAAACCCCT  TTAGGGAAAT
      CCTAACCAGA  CTC TGCTTTT  TGTATAAGAG  TTATTGGGA  AATCCCTTTA

1601  AGGCCAGGTT  TTCACCGTAA  CACGCCACAT  CTTGCGAATA  TATGTGTAGA
      TCCGGTCCAA  AAGTGGCATT  GTGCGGTGTA  GAACGCTTAT  ATACACATCT

1651  AACTGCCGGA  AATCGTCGTG  GTATTCATC  CAGAGCGATG  AAAACGTTTC
      TTGACGGCCT  TTAGCAGCAC  CATAAGTGAG  GTCTCGCTAC  TTTTGCAAAG

1701  AGTTTGCTCA  TGGAAAACGG  TGTAACAAGG  GTGAACACTA  TCCCATATCA
      TCAAACGAGT  ACCTTTTGCC  ACATTGTTC  CACTTGTGAT  AGGGTATAGT

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|       |             |             |             |             |            |
|-------|-------------|-------------|-------------|-------------|------------|
| 1751  | CCAGCTCACC  | GTCCTTTCATT | GCCATACGGA  | ACTCCGGGTG  | AGCATTCATC |
|       | GGTCGAGTGG  | CAGAAAGTAA  | CGGTATGCCCT | TGAGGCCCCAC | TCGTAAGTAG |
| 1801  | AGGCGGGCAA  | GAATGTGAAT  | AAAGGCCGGA  | TAAAACTTGT  | GCTTATTTTT |
|       | TCCGCCCGTT  | CTTACACTTA  | TTTCCGGCCT  | ATTTTGAACA  | CGAATAAAAA |
| 1851  | CTTTACGGTC  | TTTAAAAAGG  | CCGTAATATC  | CAGCTGAACG  | GTCTGGTTAT |
|       | GAAATGCCAG  | AAATTTTCC   | GGCATTTATAG | GTCGACTTGC  | CAGACCAATA |
| 1901  | AGGTACATTG  | AGCAACTGAC  | TGAAATGCCCT | CAAAATGTTT  | TTTACGATGC |
|       | TCCATGTAAC  | TCGTTGACTG  | ACTTTACGGA  | GTTTACAAG   | AAATGCTACG |
| 1951  | CATTGGGATA  | TATCAACGGT  | GGTATATCCA  | GTGATTTTTT  | TCTCCATTTT |
|       | GTAAACCCTAT | ATAGTTGCCA  | CCATATAGGT  | CACTAAAAAA  | AGAGGTAAAA |
| 2001  | AGCTTCCTTA  | GCTCCTGAAA  | ATCTCGATAA  | CTCAAAAAAT  | ACGCCCGGTA |
|       | TCGAAGGAAT  | CGAGGACTTT  | TAGAGCTATT  | GAGTTTTTTA  | TGCGGGCCAT |
| AatII |             |             |             |             |            |
| ~~~~~ |             |             |             |             |            |
| 2051  | GTGATCTTAT  | TTCATTATGG  | TGAAAGTTGG  | AACCTCACCC  | GACGTCTAAT |
|       | CACTAGAATA  | AAGTAATACC  | ACTTTCAACC  | TTGGAGTGCG  | CTGCAGATTA |
| 2101  | GTGAGTTAGC  | TCACTCATTA  | GGCACCCCCAG | GCTTTACACT  | TTATGCTTCC |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |                                                                                                                  |       |
|------|------------------------------------------------------------------------------------------------------------------|-------|
|      | CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA AATACGAAGG                                                           |       |
| 2151 | GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA<br>CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA GTGTGTCCTT |       |
|      | XbaI                                                                                                             | SphI  |
|      | ~~~~~                                                                                                            | ~~~~~ |
| 2201 | ACAGCTATGA CCATGATTAC GAATTCTAG ACCCCCCCCC CGCATGCCAT<br>TGTCGATACT GGTACTAATG CTAAAGATC TGGGGGGGGG GCGTACGGTA   |       |
|      | HindIII                                                                                                          |       |
|      | ~~~~~                                                                                                            |       |
| 2251 | AACTTCGTAT AATGTACGCT ATACGAAGTT ATAAGCTTGA CCTGTGAAGT<br>TTGAAGCATA TTACATGCCA TATGCTTCAA TATTCGAACT GGACACTTCA |       |
|      |                                                                                                                  | PacI  |
|      |                                                                                                                  | ~~~~~ |
| 2301 | GAATAATGGC GCAGATTGTG CGACATTTT TTTGTCTGCC GTTAAATTAA<br>CTTTTACC CGTCTAACAC GCTGTAAAAA AACAGACGG CAAATTAAAT     |       |
|      | FseI                                                                                                             |       |
|      | ~~~~~                                                                                                            |       |
| 2351 | GGGGGGGGC CGCCATTAT CAAAAGGAT CTCAAGAAGA TCCTTTGATC<br>CCCCCCCCG GCCGGTAATA GTTTTTCCTA GAGTCTTCT AGGAAACTAG      |       |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |                                                                                                                   |
|------|-------------------------------------------------------------------------------------------------------------------|
| 2401 | TTTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC GTTAAGGGAT<br>AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTGAGTG CAATTCCCTA  |
| 2451 | TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTAAATT<br>AAACCAGTAC TCTAATAGTT TTTCCCTAGAA GTGGATCTAG GAAATTTAA   |
| 2501 | AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT<br>TTTTTACTTC AAAATTAGT TAGATTTTCAT ATATACTCAT TTGAACCAGA  |
| 2551 | GACAGTTACC CAATGCTTAA TCAGTGAGGC ACCTATCTCA GCGATCTGTC<br>CTGTCAATGG GTTACGAATT AGTCACTCCG TGGATAGAGT CGCTAGACAG  |
| 2601 | TATTTTCGTTT ATCCATAGTT GCCTGACTCC CCGTCGTGTA GATAACTACG<br>ATAAAGCAAG TAGGTATCAA CGGACTGAGG GGCAGCACAT CTATTGATGC |
| 2651 | ATACGGGAGG GCTTACCATC TGGCCCCAGT GCTGCAATGA TACCGCGAGA<br>TATGCCCTCC CGAATGGTAG ACCGGGGTCA CGACGTTACT ATGGCGCTCT  |
| 2701 | CCCACGCTCA CCGGCTCCAG ATTTATCAGC AATAAACCAG CCAGCCGGAA<br>GGTGCGGAGT GGCCGAGGTC TAAATAGTCG TTATTGGTC GGTCCGCCCTT  |
| 2751 | GGGCCGAGCG CAGAAGTGGT CCTGCAACTT TATCCGCCCTC CATCCAGTCT<br>CCCGGCTCGC GTCTTCACCA GGACGTTGAA ATAGCGGAG GTAGGTCAGA  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |             |             |            |             |
|------|-------------|-------------|-------------|------------|-------------|
| 2801 | ATTAACTGTT  | GCCGGGAAGC  | TAGAGTAAGT  | AGTTCGCCAG | TTAATAGTTT  |
|      | TAAATTGACAA | CGGCCCTTCG  | ATCTCATTCA  | TCAAGCGGTC | AATTATCAAA  |
| 2851 | GCGCAACGTT  | GTTGCCATTG  | CTACAGGCAT  | CGTGGTGTC  | CGCTCGTCGT  |
|      | CGCGTTGCAA  | CAACGGTAAC  | GATGTCCGTA  | GCACCACAGT | GCGAGCAGCA  |
| 2901 | TTGGTATGGC  | TTCATTTCAGC | TCCGGTTCCC  | AACGATCAAG | GCGAGTTACA  |
|      | AACCATACCG  | AAGTAAGTCG  | AGGCCAAGGG  | TTGCTAGTTC | CGCTCAATGT  |
| 2951 | TGATCCCCCA  | TGTTGTGCAA  | AAAAGCGGTT  | AGCTCCTTCG | GTCCCTCCGAT |
|      | ACTAGGGGGT  | ACAACACGTT  | TTTTCGCCAA  | TCGAGGAAGC | CAGGAGGCTA  |
| 3001 | CGTTGTCAGA  | AGTAAGTTGG  | CCGCAGTGTT  | ATCACTCATG | GTTATGGCAG  |
|      | GCAACAGTCT  | TCATTCAACC  | GGCGTCACAA  | TAGTGAGTAC | CAATACCGTC  |
| 3051 | CACTGCATAA  | TTCTCTTACT  | GTCAATGCCAT | CCGTAAGATG | CTTTTCTGTG  |
|      | GTGACCGTATT | AAGAGAAATGA | CAGTACGGTA  | GCCATTCTAC | GAAAAGACAC  |
| 3101 | ACTGGTGAGT  | ACTCAACCAA  | GTCAATTCTGA | GAATAGTGA  | TGCGGCGACC  |
|      | TGACCACTCA  | TGAGTTGGTT  | CAGTAAGACT  | CTTATCACAT | ACGCCGCTGG  |
| 3151 | GAGTTGCTCT  | TGCCCGGCGT  | CAATACGGGA  | TAATACCGCG | CCACATAGCA  |
|      | CTCAACGAGA  | ACGGGCCGCA  | GTTATGCCCT  | ATTATGGCGC | GGTGATATCGT |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

| XmnI  |                                                                                                                   |
|-------|-------------------------------------------------------------------------------------------------------------------|
| ~~~~~ |                                                                                                                   |
| 3201  | GAAC TT TAAA AGTGCTCATC ATTGGAAAAC GTTCTTCGGG GCGAAACTC<br>CTTGAAATTT TCACGAGTAG TAACCTTTTG CAAGAAGCCC CGCTTTTGAG |
| 3251  | TCAAGGATCT TACCGCTGTT GAGATCCAGT TCGATGTAAC CCACTCGCGC<br>AGTTCCTAGA ATGGCGACAA CTCTAGGTCA AGCTACATTG GTGAGCGCG   |
| 3301  | ACCCAACTGA TCCTCAGCAT CTTTACTTT CACCAGCGTT TCTGGGTGAG<br>TGGGTTGACT AGGAGTCGTA GAAAATGAAA GTGGTCGCAA AGACCCACTC   |
| 3351  | CAAAACACAGG AAGGCAAAAT GCCGCAAAA AGGGAATAAG GCGACACGG<br>GTTTTTGTCC TTCCGTTTTA CGCGTTTTC TCCCTTATTC CCGCTGTGCC    |
| 3401  | AAATGTTGAA TACTCATACT CTCCTTTT CAATATTATT GAAGCATTTA<br>TTTACAACTT ATGAGTATGA GAAGGAAAA GTTATAATAA CTCGTAATA      |
| BsrGI |                                                                                                                   |
| 3451  | TCAGGGTTAT TGTCTCATGA GCGGATACAT ATTTGAAT<br>AGTCCCAATA ACAGAGTACT CGCCTATGTA TAAACTTA                            |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

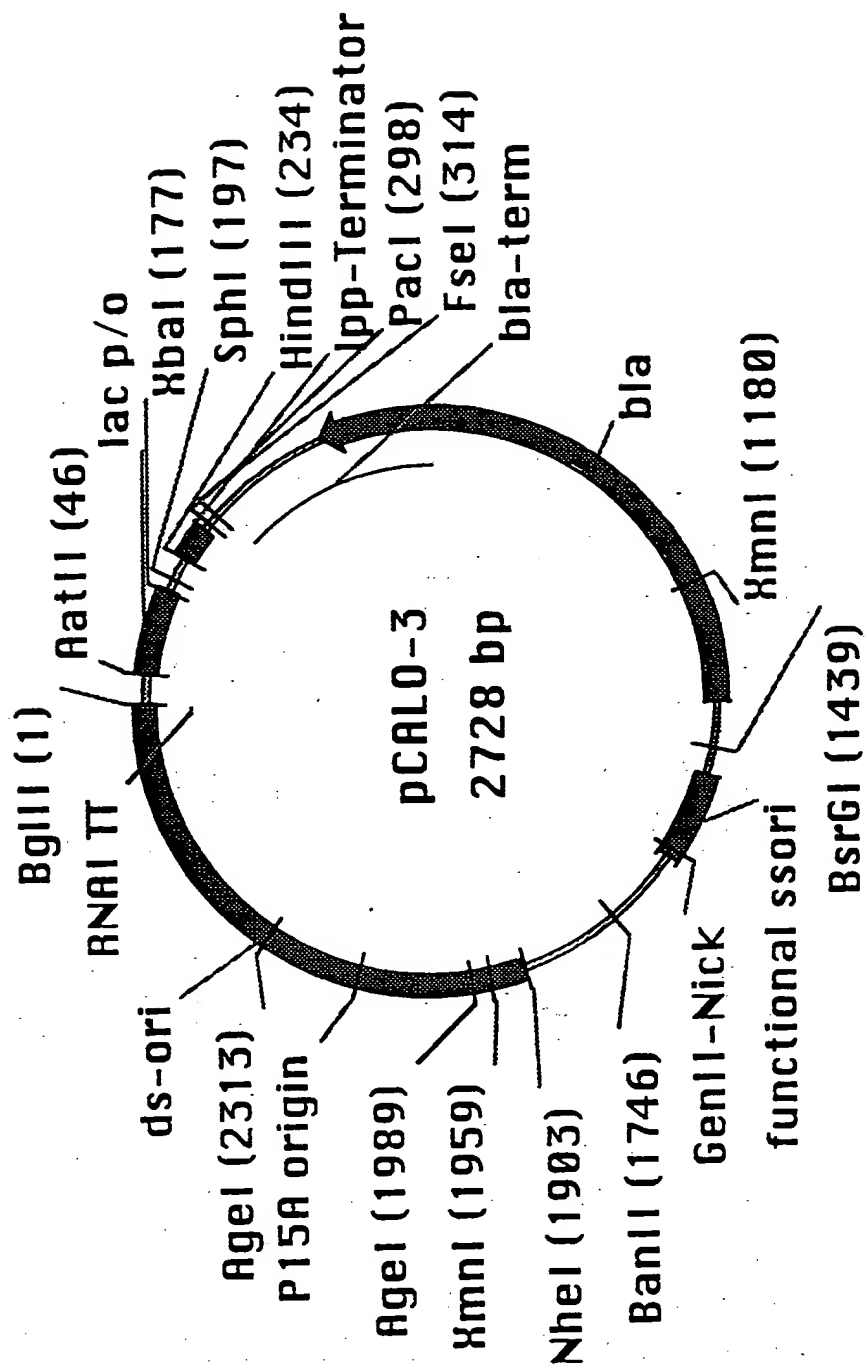


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

| pCALO-3: |                                                                                                                  |
|----------|------------------------------------------------------------------------------------------------------------------|
|          | BglII                                                                                                            |
|          | ~~~~~                                                                                                            |
| 1        | GATCTCATAA CTTCGTATAA TGTATGCTAT ACGAAGTTAT GACGTCTAAT<br>CTAGAGTATT GAAGCATATT ACATACGATA TGCTTCAATA CTGCAGATTA |
| 51       | GTGAGTTAGC TCACTCATTG GGCACCCAG GCTTTACTT TATGCTTCC<br>CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA AATACGAAGG    |
| 101      | GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATT CACACAGGAA<br>CCGAGCATAC AACACACCTT AACACTCGCC TATTGTTAAA GTGTGTCCTT  |
|          | XbaI                                                                                                             |
|          | ~~~~~                                                                                                            |
| 151      | ACAGCTATGA CCATGATTAC GAATTCTAG ACCCCCCCCC CGCATGCCAT<br>TGTCGATACT GGTAATAATG CTTAAAGATC TGGGGGGGGG GCGTACGGTA  |
|          | HindIII                                                                                                          |
|          | ~~~~~                                                                                                            |
| 201      | AACTTCGTAT AATGTACGCT ATACGAAGTT ATAAGCTTGA CCTGTGAAGT<br>TTGAAGCATA TTACATGCCG TATGCTTCAA TATTGGAAC GGACACTTCA  |
|          | PacI                                                                                                             |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

```

~~~~~
251  GAAAAATGGC GCAGATTGTG CGACATTTT TTTGTCTGCC GTTTAATTAA
    CTTTATTACCG CGTCTAACAC GCTGTAAAAA AACACAGACGG CAAATTAATT

      FseI
      ~~~~~
301  GGGGGGGGC CGCCATTAT CAAAAGGAT CTCAAGAAGA TCCTTTGATC
    CCCCCCCCG GCCGGTAATA GTTTTCCCTA GAGTTCCTCT AGGAAACTAG

351  TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC GTTAAGGGAT
    AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTGTGAGTG CAATTCCCTA

401  TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTAAATT
    AAACCAGTAC TCTAATAGTT TTTCCCTAGAA GTGGATCTAG GAAAATTTAA

451  AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
    TTTTACTTC AAAATTAGT TAGATTTCAT ATATACTCAT TTGAACCAGA

501  GACAGTTACC CAATGCTTAA TCAGTGAGGC ACCTATCTCA GCGATCTGTC
    CTGTCAATGG GTTACGAATT AGTCACTCCG TGGATAGAGT CGCTAGACAG

551  TATTTCGTTC ATCCATAGTT GCCTGACTCC CCGTCGTGTA GATAACTACG
    ATAAAGCAAG TAGTATCAA CGGACTGAGG GGCAGCACAT CTATTGATGC

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|     |            |             |             |             |             |
|-----|------------|-------------|-------------|-------------|-------------|
| 601 | ATACGGGAGG | GCTTACCATC  | TGGCCCCCAGT | GCTGCAATGA  | TACCGCGAGA  |
|     | TATGCCCTCC | CGAATGGTAG  | ACCGGGGTCA  | CGACGTTACT  | ATGGCGCTCT  |
| 651 | CCCACGCTCA | CCGGCTCCAG  | ATTATCAGC   | AATAAACCCAG | CCAGCCGGAA  |
|     | GGTGCGAGT  | GGCCGAGGTC  | TAAATAGTCG  | TTATTGGTC   | GGTCGGCCTT  |
| 701 | GGGCCGAGCG | CAGAAGTGGT  | CCTGCAACTT  | TATCCGCCCTC | CATCCAGTCT  |
|     | CCCGGCTCGC | GTCTTCACCA  | GGACGTTGAA  | ATAGCGGAG   | GTAGGTCAGA  |
| 751 | ATTAACTGTT | GCCGGGAAGC  | TAGAGTAAGT  | AGTTCGCCCAG | TTAATAGTTT  |
|     | TAATTGACAA | CGGCCCTTCG  | ATCTCATTCA  | TCAAGCGGTC  | AATTATCAAA  |
| 801 | GCGCAACGTT | GTTGCCATTG  | CTACAGGCAT  | CGTGGTGTCA  | CGCTCGTCGT  |
|     | CGCGTTGCAA | CAACGGTAAC  | GATGTCCGTA  | GCACCACAGT  | GCGAGCAGCA  |
| 851 | TTGGTATGGC | TTCAATTCAGC | TCCGGTTCCC  | AACGATCAAG  | GCGAGTTACA  |
|     | AACCATACCG | AAGTAAGTCG  | AGGCCAAGGG  | TTGCTAGTTC  | CGCTCAATGT  |
| 901 | TGATCCCCCA | TGTTGTGCAA  | AAAAGCGGTT  | AGCTCCTTCG  | GTCCCTCCGAT |
|     | ACTAGGGGGT | ACAACACGTT  | TTTTTCGCCAA | TCGAGGAAGC  | CAGGAGGCTA  |
| 951 | CGTTGTCAGA | AGTAAGTTGG  | CCGCAGTGTT  | ATCACTCATG  | GTTATGGCAG  |
|     | GCAACAGTCT | TCATTCAACC  | GGCGTCACAA  | TAGTGAGTAC  | CAATACCGTC  |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |             |             |            |            |
|------|-------------|-------------|-------------|------------|------------|
| 1001 | CACTGCATAA  | TTCCTCTTACT | GTCAATGCCAT | CCGTAAGATG | CTTTTCTGTG |
|      | GTGACGTATT  | AAGAGAAATGA | CAGTACGGTA  | GGCATTCTAC | GAAAAGACAC |
| 1051 | ACTGGTGAGT  | ACTCAACCAA  | GTCAATCTGA  | GAATAGTGTA | TGCGGCGACC |
|      | TGACCACTCA  | TGAGTTGGTT  | CAGTAAGACT  | CTTATCACAT | ACGCCGCTGG |
| 1101 | GAGTTGCTCT  | TGCCCGGCGT  | CAATACGGGA  | TAATACCGCG | CCACATAGCA |
|      | CTCAACGAGA  | ACGGGCCGCA  | GTTATGCCCT  | ATTATGGCGC | GGTGATCGT  |
|      |             |             | XmnI        |            |            |
|      |             |             | ~~~~~       |            |            |
| 1151 | GAACTTTAA   | AGTGCTCATC  | ATTGGAAAAC  | GTTCTTCGGG | GCGAAAACTC |
|      | CTTGAAATTT  | TCACGAGTAG  | TAACCTTTTG  | CAAGAAGCCC | CGCTTTTGAG |
| 1201 | TCAAGGATCT  | TACCGCTGTT  | GAGATCCAGT  | TCGATGTAAC | CCACTCGCGC |
|      | AGTTCCTAGA  | ATGGCGACAA  | CTCTAGGTCA  | AGCTACATTG | GGTGAGCGCG |
| 1251 | ACCCAACCTGA | TCCTCAGCAT  | CTTTTACTTT  | CACCAGCGTT | TCTGGGTGAG |
|      | TGGGTTGACT  | AGGAGTCGTA  | GAAAATGAAA  | GTGGTCGCAA | AGACCCACTC |
| 1301 | CAAAAACAGG  | AAGGCAAAAT  | GCCGCAAAA   | AGGGAATAAG | GCGACACGG  |
|      | GTTTTTGTCC  | TTCCCGTTT   | CGCGTTTTT   | TCCCTTATTC | CCGCTGTGCC |
| 1351 | AAATGTTGAA  | TACTCATACT  | CTTCCTTTT   | CAATATTATT | GAAGCATTTA |

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |             |            |             |             |             |
|------|-------------|------------|-------------|-------------|-------------|
|      | TTTACAACCTT | ATGAGTATGA | GAAGGAAAAA  | GTTATAATAA  | CTTCGGTAAAT |
|      | BsrGI       |            |             |             |             |
|      | ~~~~~       |            |             |             |             |
| 1401 | TCAGGGTTAT  | TGTCTCATGA | GCGGATACAT  | ATTTGAATGT  | ACATGAAATT  |
|      | AGTCCCAATA  | ACAGAGTACT | CGCCTATGTA  | TAAACTTACA  | TGTACTTTAA  |
| 1451 | GTAACGTTA   | ATATTTTGTT | AAAATTCCGG  | TTAAATTTT   | GTTAAATCAG  |
|      | CATTTGCAAT  | TATAAAACAA | TTTTAAGCGC  | AATTTAAAA   | CAATTTAGTC  |
| 1501 | CTCATTTTTT  | AACCAATAGG | CCGAAATCGG  | CAAAATCCCT  | TATAAATCAA  |
|      | GAGTAAAAAA  | TTGGTTATCC | GGCTTTAGCC  | GTTTTAGGGA  | ATATTTAGTT  |
| 1551 | AAGAAATAGAC | CGAGATAGGG | TTGAGTGTTG  | TTCCAGTTTG  | GAACAAGAGT  |
|      | TTCTTATCTG  | GCTCTATCCC | AACTCACAAAC | AAGGTCAAAC  | CTTGTTCTCA  |
| 1601 | CCACTATTAA  | AGAACGTGGA | CTCCAACGTC  | AAAGGGCGAA  | AAACCGTCTA  |
|      | GGTGATAATT  | TCTTGCACCT | GAGGTTGCAG  | TTTCCCGCCTT | TTTGGCAGAT  |
| 1651 | TCAGGGCGAT  | GGCCCACTAC | GAGAACCATC  | ACCCTAATCA  | AGTTTTTGG   |
|      | AGTCCCGCTA  | CCGGGTGATG | CTCTTGGTAG  | TGGGATTAGT  | TCAAAAAAAC  |
|      | BanII       |            |             |             |             |
|      | ~~~~~       |            |             |             |             |



Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|      |                                                                                          |                     |                     |                     |                       |
|------|------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|-----------------------|
| 1701 | G G T C G A G G T G                                                                      | C C G T A A A G C A | C T A A A T C G G A | A C C C T A A A G G | G A G C C C C C G A   |
|      | C C A G C T C C A C                                                                      | G G C A T T T C G T | G A T T A G C C T   | T G G G A T T T C C | C T C G G G G G C T   |
| 1751 | T T T A G A G C T T                                                                      | G A C G G G A A A   | G C C G G C G A A C | G T G G C G A G A A | A G G A A G G G A A   |
|      | A A A T C T C G A A                                                                      | C T G C C C C T T T | C G C C G C T T G   | C A C C G C T C T T | T C C T T C C C C T T |
| 1801 | G A A G C G A A A                                                                        | G G A G C G G C G   | C T A G G G C G C T | G G C A A G T G T A | G C G G T C A C G C   |
|      | C T T T C G C T T T                                                                      | C C T C G C C C G C | G A T C C C G C G A | C C G T T C A C A T | C G C C A G T G C G   |
| 1851 | T G C G C G T A A C                                                                      | C A C C A C A C C C | G C C G C G C T T A | A T G C G C C G C T | A C A G G G C G C G   |
|      | A C G C G C A T T G                                                                      | G T G G T G T G G G | C G C G C G G A A T | T A C G C G G C G A | T G T C C C C G C G C |
|      | <div style="text-align: center;">NheI</div> <div style="text-align: center;">~~~~~</div> |                     |                     |                     |                       |
| 1901 | T G C T A G C G G A                                                                      | G T G T A T A C T G | G C T T A C T A T G | T T G G C A C T G A | T G A G G G T G T C   |
|      | A C G A T C G C C T                                                                      | C A C A T A T G A C | C G A A T G A T A C | A A C C G T G A C T | A C T C C C A C A G   |
|      | <div style="text-align: center;">XmnI</div> <div style="text-align: center;">~~~~~</div> |                     |                     |                     |                       |
| 1951 | A G T G A A G T G C                                                                      | T T C A T G T G G C | A G G A G A A A A A | A G G C T G C A C C | G G T G C G T C A G   |
|      | T C A C T T C A C G                                                                      | A A G T A C A C C G | T C C T C T T T T T | T C C G A C G T G G | C C A C G C A G T C   |
| 2001 | C A G A A T A T G T                                                                      | G A T A C A G G A T | A T A T T C C G C T | T C C T C G C T C A | C T G A C T C G C T   |
|      | G T C T T A T A C A                                                                      | C T A T G T C C T A | T A T A A G G C G A | A G G A G C G A G T | G A C T G A G C G A   |

AgeI

~~~~~

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|               |             |            |            |            |             |
|---------------|-------------|------------|------------|------------|-------------|
| 2051          | ACGCTCGGTC  | GTTGACTGC  | GGCAGCGGA  | AATGGCTTAC | GAACGGGGCG  |
|               | TGCGAGCCAG  | CAAGCTGACG | CCGCTCGCCT | TTACCGAATG | CTTGCCCCCGC |
| 2101          | GAGATTTCCT  | GGAAGATGCC | AGGAAGATAC | TTAACAGGGA | AGTGAGAGGG  |
|               | CTCTAAAGGA  | CCTTCTACGG | TCCTTCTATG | AATTGTCCCT | TCACTCTCCC  |
| 2151          | CCGCGGCAAA  | GCCGTTTTC  | CATAGGCTCC | GCCCCCCTGA | CAAGCATCAC  |
|               | GGCGCCGTTT  | CGGCAAAAAG | GTATCCGAGG | CGGGGGGACT | GTTCGTAGTG  |
| 2201          | GAAATCTGAC  | GCTCAAATCA | GTGGTGGCGA | AACCCGACAG | GACTATAAAG  |
|               | CTTTAGACTG  | CGAGTTTAGT | CACCACCGCT | TTGGGCTGTC | CTGATATTTC  |
| 2251          | ATACCAGGCG  | TTTCCCCCTG | GCGGCTCCCT | CCTGCGCTCT | CCTGTTCCCTG |
|               | TATGGTCCGC  | AAAGGGGGAC | CGCCGAGGGA | GGACGCGAGA | GGACAAGGAC  |
| AgeI<br>~~~~~ |             |            |            |            |             |
| 2301          | CCTTTCGGTT  | TACCGGTGTC | ATTCCGCTGT | TATGGCCGCG | TTTGTCTCAT  |
|               | GGAAAGCCAA  | ATGGCCACAG | TAAGGCGACA | ATACCGGCGC | AAACAGAGTA  |
| 2351          | TCCACGCCCTG | ACACTCAGTT | CCGGGTAGGC | AGTTCGCTCC | AAGCTGGACT  |
|               | AGGTGCGGAC  | TGTGAGTCAA | GGCCCATCCG | TCAAGCGAGG | TTCGACCTGA  |

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

|       |            |             |            |            |            |
|-------|------------|-------------|------------|------------|------------|
| 2401  | GTATGCACGA | ACCCCCCGTT  | CAGTCCGACC | GCTGCGCCTT | ATCCGGTAAC |
|       | CATACGTGCT | TGGGGGGCAA  | GTCAGGCTGG | CGACGCGGAA | TAGGCCATTG |
| 2451  | TATCGTCTTG | AGTCCAACCC  | GGAAAGACAT | GCAAAAGCAC | CACTGGCAGC |
|       | ATAGCAGAAC | TCAGGTTGGG  | CCTTTCTGTA | CGTTTTCGTG | GTGACCGTCG |
| 2501  | AGCCACTGGT | AATTGATTTA  | GAGAGTTAG  | TCTTGAAGTC | ATGCGCCGGT |
|       | TCGGTGACCA | TTAACTAAAT  | CTCCTCAATC | AGAACTTCAG | TACGCGGCCA |
| 2551  | TAAGGCTAAA | CTGAAAGGAC  | AAGTTTTAGT | GACTGCGCTC | CTCCAAGCCA |
|       | ATTCCGATTT | GACTTTCCCTG | TTCAAAATCA | CTGACGCGAG | GAGGTTCCGT |
| 2601  | GTTACCTCGG | TTCAAAGAGT  | TGGTAGCTCA | GAGAACCTAC | GAAAACCCG  |
|       | CAATGGAGCC | AAGTTTCTCA  | ACCATCGAGT | CTCTTGGATG | CTTTTGGCG  |
| 2651  | CCTGCAAGGC | GGTTTTTTTCG | TTTTCAGAGC | AAGAGATTAC | GCGCAGACCA |
|       | GGACGTTCCG | CCAAAAAAGC  | AAAAGTCTCG | TTCTCTAATG | CGCGTCTGGT |
| BglII |            |             |            |            |            |
| 2701  | AAACGATCTC | AAGAAGATCA  | TCTTATTA   |            |            |
|       | TTTGCTAGAG | TTCTTCTAGT  | AGAAATAAT  |            |            |

Figure 35b: List of oligonucleotides used for synthesis of modules

M1: PCR using template

NoVspAatII: TAGACGTC

M2: synthesis

BloxA-A: TATGAGATCTCATAACTTCGTATAATGTACGCTATACG-  
AAGTTAT

BloxA-B: TAATAACTTCGTATAGCATACATTATACGAAGTTATG-  
AGATCTCA

M3: PCR, NoVspAatII as second oligo

XloxS-muta: CATTTTTGCCCTCGTTATCTACGCATGCGATAACTTCGTA-  
TAGCGTACATTATACGAAGTTATTCTAGACATGGTCATAGCTGTTTCCTG

M7-I: PCR

gIIIINEW-fow: GGGGGGAATTCGGTGGTGGTGGATCTGCGTGCGCTG-  
AAACGGTTGAAAGTTG

gIIIINEW-rev: CCCCCCAAGCTTATCAAGACTCCTTATTACG

M7-II: PCR

gIIIss-fow: GGGGGGGGAATTCGGAGGCGGTCCGGTGGTGGC

M7-III: PCR

gIIIsupernew-fow: GGGGGGGGAATTCGAGCAGAAGCTGATCTCT-  
GAGGAGGATCTGTAGGGTGGTGGCTCTGGTCCGGTGATTTG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M8: synthesis

lox514-A: CCATAACTTCGTATAATGTACGCTATACGAAGTTATA

lox514-B: AGCTTATAACTTCGTATAGCGTACATTATACGAAGT-  
TATGGCATG

M9II: synthesis

M9II-fow: AGCTTGACCTGTGAAGTGAAAAATGGCGCAGATT-  
GTGCGACATTTTTTTGTCTGCCGTTTAATTAAAGGGGGGGT

M9II-rev: GTACACCCCCCCCCAGGCCGGCCCCCCCCCCCCCTTAA-  
TTAAACGGCAGACAAAAAAAATGTCGCACAATCTGCG

M10II: assembly PCR with template

bla-fow: GGGGGGGTGTACATTCAAATATGTATCCGCTCATG

bla-seq4: GGGTTACATCGAACTGGATCTC

bla1-muta: CCAGTTCGATGTAACCCACTCGCGCACCCAACTGATC-  
CTCAGCATCTTTACTTTCACC

blaII-muta: ACTCTAGCTTCCCGGCAACAGTTAATAGACTGGATG-  
GAGGCGG

bla-NEW: CTGTTGCCGGGAAGCTAGAGTAAG

bla-rev: CCCCCCTTAATTAAGGGGGGGGGCCGGCCATTATCAAA-  
AAGGATCTCAAGAAGATCC

M11II/III: PCR, site-directed mutagenesis

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

f1-fow: GGGGGGGGCTAGCACGCGCCCTGTAGCGGCGCATTA

f1-rev: CCCCCCTGTACATGAAATTGTAAACGTTAATATTTTG

f1-t133.muta: GGGCGATGGCCCACTACGAGAACCATCACCTAATC

M12: assembly PCR using template

p15-fow: GGGGGGAGATCTAATAAGATGATCTTCTTGAG

p15-NEWI: GAGTTGGTAGCTCAGAGAACCTACGAAAAACCGCCCTG-  
CAAGGCG

p15-NEWII: GTAGGTTCTCTGAGCTACCAACTC

p15-NEWIII: GTTCCCCCTGGCGGCTCCCTCCTGCGCTCTCCTGTTCT-  
GCC

p15-NEWIV: AGGAGGGAGCCGCCAGGGGGAAAC

p15-rev: GACATCAGCGCTAGCGGAGTGTATAC

M13: synthesis

BloxXB-A: GATCTCATAACTTCGTATAATGTATGCTATACGAAGTTA-  
TTCA

BloxXB-B: GATCTGAATAACTTCGTATAGCATACATTATACGAAGTTA-  
TGAGA

M14-Ext2: PCR, site-directed mutagenesis

ColEXT2-fow: GGGGGGGGAGATCTGACCAAAATCCCTTAACGTGAG

Col-mutal: GGTATCTGCGCTCTGCTGTAGCCAGTTACCTTCGG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

Col-rev: CCCCCCGCTAGCCATGTGAGCAAAAGGCCAGCAA

M17: assembly PCR using template

CAT-1: GGGACGTCGGGTGAGGTTCCAAC

CAT-2: CCATACGGAACCTCCGGGTGAGCATTTCATC

CAT-3: CCGGAGTTCCGTATGG

CAT-4: ACGTTTAAATCAAACTGG

CAT-5: CCAGTTTTGATTAAACGTAGCCAATATGGACAACTTCTTC-  
GCCCCGTTTTCACTATGGGCAAATATT

CAT-6: GGAAGATCTAGCACCAGGCGTTTAAG

M41: assembly PCR using template

LAC1: GAGGCCGGCCATCGAATGGCGCAAAAC

LAC2: CGCGTACCGTCCTCATGGGAGAAAATAATAC

LAC3: CCATGAGGACGGTACGCGACTGGGCGTGGAGCATCTGGTCGCA-  
TTGGGTCACCAGCAAATCCGCTGTTAGCTGGCCCATTAAG

LAC4: GTCAGCGGCGGGATATAACATGAGCTGTCCTCGGTATCGTCG

LAC5: GTTATATCCCGCCGCTGACCACCATCAAAC

LAC6: CATCAGTGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGT4TTG-  
GGAGCCAGGGTGGTTTTTC

LAC7: GGTTAATTAACTCACTGCCCGCTTTCAGTCGGGAAACCTGTCGTGCC-  
AGCTGCATCAGTGAATCGGCCAAC

M41-MCS-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGGCTT-  
AAGGGGGGGGGGGG

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M41-MCS-rev: CTAGCCCCCCCCCCCCCTTAAGCCCCCCCCCGGTCCGGT-TTAAACACTAGT

M41-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGCTTAA-GGGGGGGGGGGG

M41-rev: CCCCCCTTAAGTGGGCTGCAAAACAAAACGGCCTCC-TGTCAGGAAGCCGCTTTATCGGGTAGCCTCACTGCCCGCTTCC

M41-A2: GTTGTTGTGCCACGCGGTTAGGAATGTAATTCAGCTCCGC

M41-B1: AACCGCGTGGCACAACAAC

M41-B2: CTCGTTCTACCATCGACACGACCACGCTGGCACCCAGTTG

M41-C1: GTGTCGATGGTAGAACGAAG

M41-CII: CCACAGCAATAGCATCCTGGTCATCCAGCGGATAGTT-AATAATCAGCCCACTGACACGTTGCGCGAG

M41-DI: GACCAGGATGCTATTGCTGTGG

M41-DII: CAGCGCGATTGCTGGTGGCCCAATGCGACCAGATGC

M41-EI: CACCAGCAAATCGCGCTG

M41-EII: CCCGGACTCGGTAATGGCACGCATTGCGCCCAGCGCC

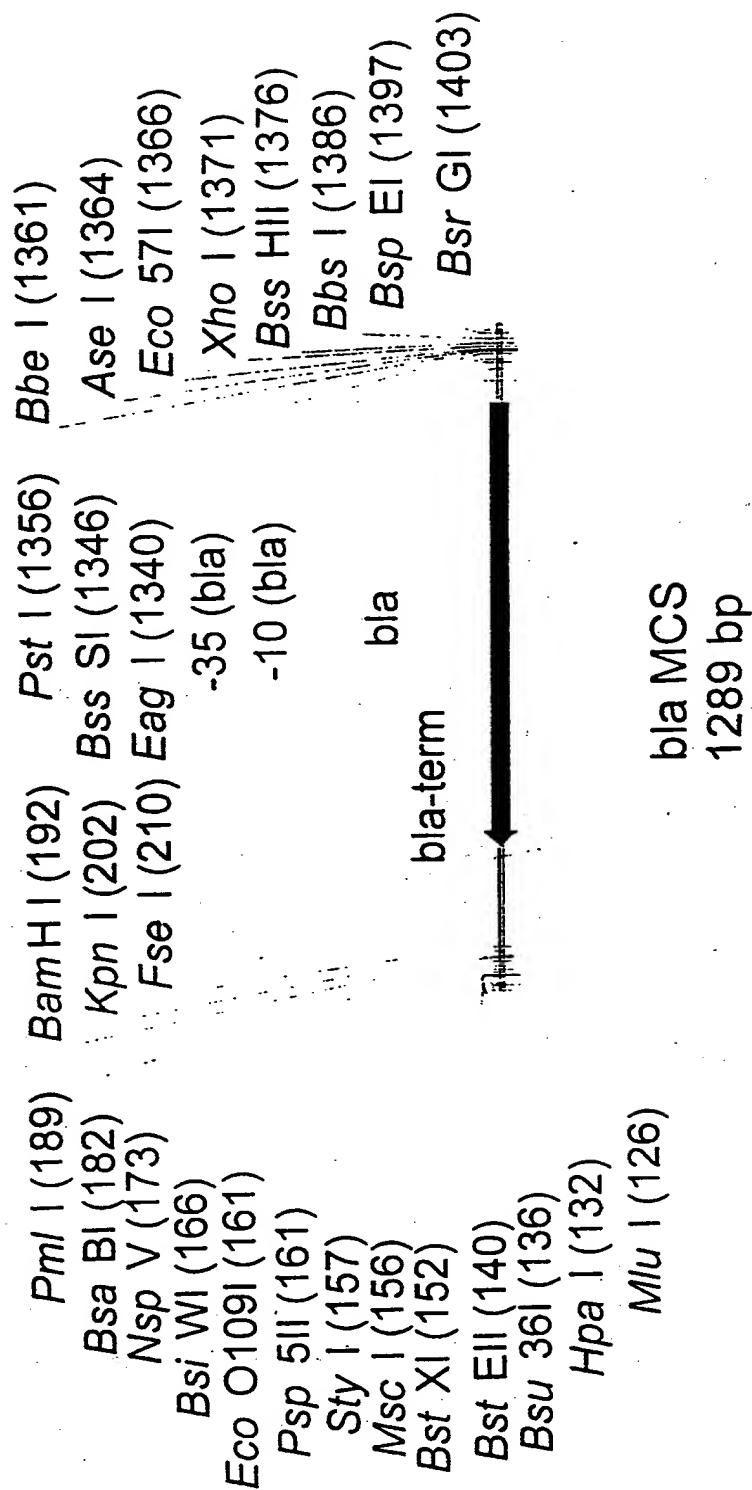
M41-FI: GCCATTACCGAGTCCGGG

M42: synthesis

Eco-H5-Hind-fow: AATCCACCATCATCACCATTGACGTCTA

Eco-H5-Hind-rev: AGCTTAGACGTCAATGGTGATGATGGTGG



Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module

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Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

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StyI
~~~~~
Psp5II
~~~~~
EcoO109I
~~~~~
MluI   Bsu36I   BstXI   MscI   BsiWI NspV
~~~~~
HpaI   BstEII
~~~~~
126  CGCGTTAACC TCAGGTGACC AAGCCCCTGG CCAAGGTCCC GTACGTTCGA
      GCGCAATTGG AGTCCACTGG TTCGGGGACC GGTCCAGGG CATGCAAGCT

PmlI
~~~~~
NspVBsaBI   BamHI   KpnI   FseI
~~~~~
176  AGATTACCAT CACGTGGATC CGTACCAGG CCGGCCATTA TCAAAAAGGA
      TCTAATGGTA GTGCACCTAG GCCATGGTCC GGCCGGTAAT AGTTTTCCT

226  TCTCAAGAAG ATCCTTTGAT CTTTCTACG GGGTCTGACG CTCAGTGGAA
      AGAGTTCCTC TAGGAAACTA GAAAGATGC CCCAGACTGC GAGTCACCTT

276  CGAAAACTCA CGTTAAGGGA TTTTGGTCAT GAGATTATCA AAAAGGATCT
      GCTTTTGAGT GCAATTCCCT AAAACCAGTA CTCTAATAGT TTTTCCTAGA

```

Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

|     |             |            |            |             |             |
|-----|-------------|------------|------------|-------------|-------------|
| 326 | TCACCTAGAT  | CCTTTTAAAT | TAAAAATGAA | GTTTTAAATC  | AATCTAAAGT  |
|     | AGTGGATCTA  | GGAAAAATTA | ATTTTACTT  | CAAAATTTAG  | TTAGATTTCA  |
| 376 | ATATATGAGT  | AAACTTGGTC | TGACAGTTAC | CAATGCTTAA  | TCAGTGAGGC  |
|     | TATATACTCA  | TTTGAACCAG | ACTGTCAATG | GTTACGAATT  | AGTCACTCCG  |
| 426 | ACCTATCTCA  | GGATCTGTC  | TATTTCGTTT | ATCCATAGTT  | GCCTGACTCC  |
|     | TGGATAGAGT  | CGCTAGACAG | ATAAAGCAAG | TAGGTATCAA  | CGGACTGAGG  |
| 476 | CCGTCGTGTA  | GATAACTACG | ATACGGGAGG | GCTTACCATC  | TGGCCCCAGT  |
|     | GGCAGCACAT  | CTATTGATGC | TATGCCCTCC | CGAATGGTAG  | ACCGGGGTCA  |
| 526 | GCTGCAATGA  | TACCGCGAGA | CCCACGCTCA | CCGGCTCCAG  | ATTTATCAGC  |
|     | CGACGTTACT  | ATGGCGCTCT | GGTGCCGAGT | GGCCGAGGTC  | TAAATAGTCC  |
| 576 | AATAAACCCAG | CCAGCCGGAA | GGCCCGAGCG | CAGAAAGTGGT | CCTGCAACTT  |
|     | TTATTGGTC   | GGTCGGCCTT | CCCGGCTCGC | GTCTTCACCA  | GGACGTTGAA  |
| 626 | TATCCGCCCTC | CATCCAGTCT | ATTAAGTGT  | GCCGGGAAGC  | TAGAGTAAGT  |
|     | ATAGCGCGAG  | GTAGGTCAGA | TAATTGACAA | CGGCCCTTCG  | ATCTCATTTCA |
| 676 | AGTTCGCCCAG | TTAATAGTTT | GCGCAACGTT | GTTGCCATTG  | CTACAGGCAT  |
|     | TCAAGCGGTC  | AATTATCAAA | CGCGTTGCAA | CAACGGTAAC  | GATGTCCGTA  |

Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

|      |             |             |            |             |             |
|------|-------------|-------------|------------|-------------|-------------|
| 726  | CGTGGTGTCA  | CGCTCGTCGT  | TTGGTATGGC | TTCATTTCAGC | TCCGGTTCCC  |
|      | GCACCCACAGT | GCGAGCAGCA  | AACCATACCG | AAGTAAGTCG  | AGGCCAAGGG  |
| 776  | AACGATCAAG  | GCGAGTTACA  | TGATCCCCCA | TGTTGTGCAA  | AAAAGCGGTT  |
|      | TTGCTAGTTC  | CGCTCAATGT  | ACTAGGGGGT | ACAACACGTT  | TTTTTCGCCAA |
| 826  | AGCTCCTTCG  | GTCCCTCCGAT | CGTTGTCAGA | AGTAAGTTGG  | CCGCAGTGTT  |
|      | TCGAGGAAGC  | CAGGAGGCTA  | GCAACAGTCT | TCATTCAACC  | GGCGTCACAA  |
| 876  | ATCACTCATG  | GTTATGGCAG  | CACGTCATAA | TTCTCTTACT  | GTCATGCCAT  |
|      | TAGTGAGTAC  | CAATACCGTC  | GTGACGTATT | AAGAGAATGA  | CAGTACGGTA  |
| 926  | CCGTAAGATG  | CTTTTCTGTG  | ACTGGTGAGT | ACTCAACCAA  | GTCATTCTGA  |
|      | GGCATCTCTAC | GAAAAGACAC  | TGACCACTCA | TGAGTTGGTT  | CAGTAAGACT  |
| 976  | GAATAGTGTA  | TGCGGCGACC  | GAGTTGCTCT | TGCCCCGGCGT | CAATACGGGA  |
|      | CTTATCACAT  | ACGCCGCTGG  | CTCAACGAGA | ACGGGCCGCA  | GTTATGCCCT  |
| 1026 | TAATACCGCG  | CCACATAGCA  | GAACTTTAAA | AGTGCTCATC  | ATTGGAAAAC  |
|      | ATTATGGCGC  | GGTGATCGT   | CTTGAAATT  | TCACGAGTAG  | TAACCTTTTG  |
| 1076 | GTTCTTCGGG  | GCGAAAACATC | TCAAGGATCT | TACCGCTGTT  | GAGATCCAGT  |
|      | CAAGAAGCCC  | CGCTTTTGAG  | AGTTCCTAGA | ATGGCGACAA  | CTCTAGGTCA  |

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Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

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1126  TCGATGTAAC  CCACTCGTGC  ACCCAACTGA  TCTTCAGCAT  CTTTACTTTT
      AGCTACATTG  GTGAGCACG  TGGGTTGACT  AGAAGTCGTA  GAAATGAAA
      BSSI      Eco57I
      ~~~~~

1176  CACCAGCGTT  TCTGGGTGAG  CAAAACAGG  AAGGCAAAAT  GCCGCAAAA
      GTGGTCGCAA  AGACCCACTC  GTTTTGTGCC  TTCCGTTTTA  CGCGTTT
      ~~~~~

1226  AGGGAATAAG  GCGACACGG  AAATGTTGAA  TACTCATACT  CTTCCTTT
      TCCCTTATTC  CCGCTGTGCC  TTTACAACCT  ATGAGTATGA  GAAGGAAA
      ~~~~~

1276  CAATATTATT  GAAGCATTTA  TCAGGGTTAT  TGTCTCATGA  GCGATACAT
      GTTATAATAA  CTTCGTAAAT  AGTCCCAATA  ACAGAGTACT  CGCCTATGTA
      ~~~~~

      PstI      XhoI
      ~~~~~

      EagI  BssSI  BbeI  AseI  BshII
      ~~~~~

1326  ATTTGAATGT  ACTCGGCCGC  ACGAGCTGCA  GCGCCATTA  ATGGCTCGAG
      TAAACTTACA  TGAGCCGCGG  TGCTCGACGT  CCGCGGTAAT  TACCGAGCTC
      ~~~~~

      BshII      BspEI  BsrGI
      ~~~~~

```

Figure 36: functional map and sequence of  $\beta$ -lactamase-MCS module (continued)

|      |            |            |            |           |
|------|------------|------------|------------|-----------|
| 1376 | CGCGCTTCAG | CGCTTTGTCT | TCCGGATGTA | CATGAAATT |
|      | GCGCGAAGTC | GCGAAACAGA | AGGCCTACAT | GTACTTTAA |
|      | ECO57I     | BbsI       |            |           |
|      | ~~~~~      | ~~~~~      |            |           |

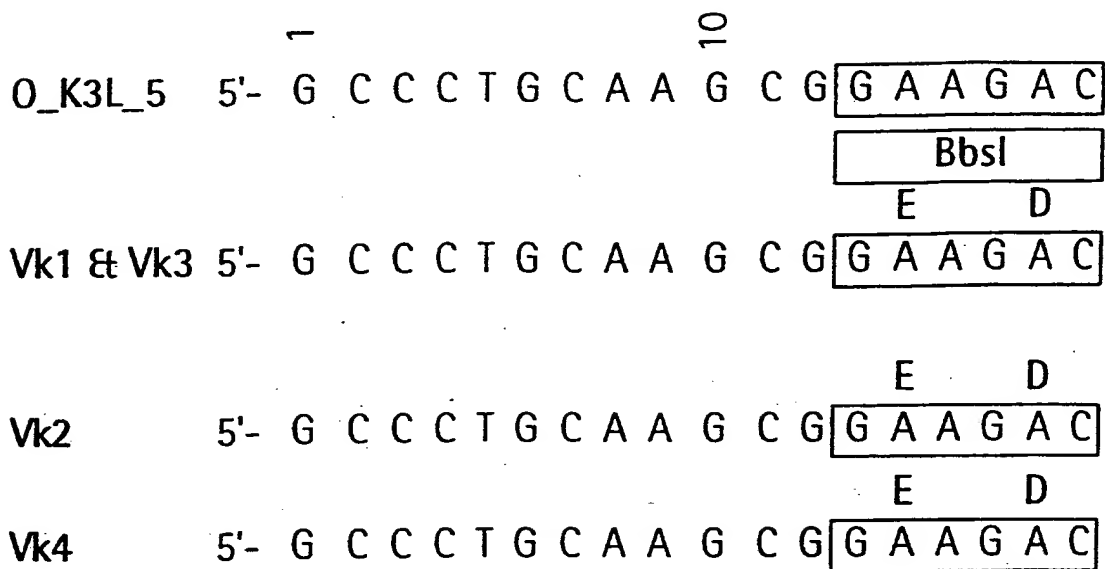
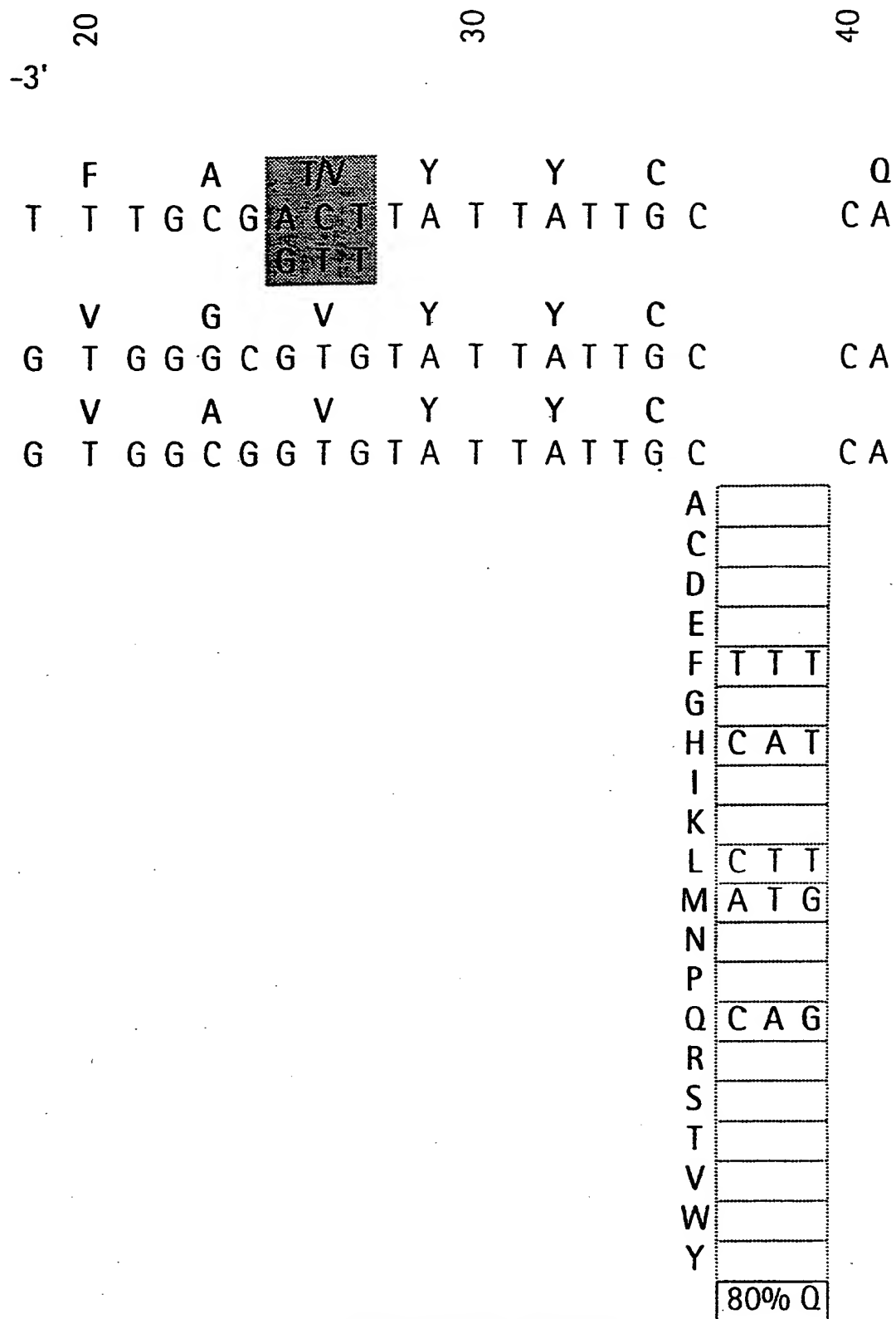
Figure 37: Oligo and primer design for V $\kappa$  CDR3 libraries

Figure 37: Oligo and primer design for V $\kappa$  CDR3 libraries

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Figure 38: Oligo and primer design for V $\lambda$  CDR3 libraries

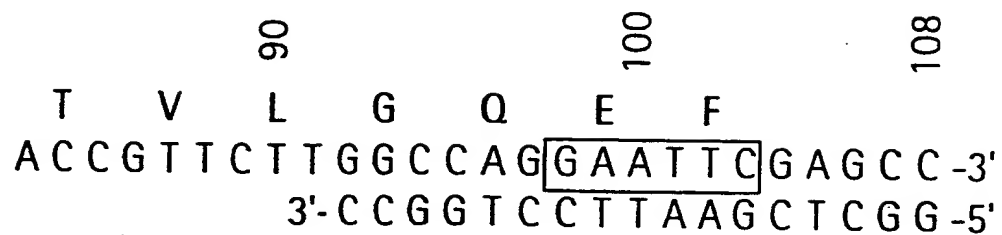
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|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|

SUBSTITUTE SHEET (RULE 26)

Figure 38: Oligo and primer design for V $\lambda$  CDR3 libraries

|    |    |    |    |     |   |   |   |     |    |          |          |   |   |    |   |   |   |   |   |   |   |   |
|----|----|----|----|-----|---|---|---|-----|----|----------|----------|---|---|----|---|---|---|---|---|---|---|---|
|    |    |    |    | 60  |   |   |   |     | 70 |          |          |   |   | 80 |   |   |   |   |   |   |   |   |
|    |    |    |    |     |   |   |   | G   | G  | G        | T        | K | L |    |   |   |   |   |   |   |   |   |
|    |    |    |    |     |   |   |   | G   | G  | C        | G        | G | C | A  | C | G | A | A | G | T | T | A |
| -  | G  | C  | T  | gap | G | C | T | gap | G  | C        | T        | G | C | T  |   |   |   |   |   |   |   |   |
| G  | A  | T  | G  | A   | T | G | A | T   | G  | A        | T        | G | A | T  |   |   |   |   |   |   |   |   |
| G  | A  | G  | G  | A   | G | G | A | G   | G  | A        | G        | G | A | G  |   |   |   |   |   |   |   |   |
| T  | T  | T  | T  | T   | T | T | T | T   | T  | T        | T        | T | T | T  |   |   |   |   |   |   |   |   |
| G  | G  | T  | G  | G   | T | G | G | T   | G  | G        | T        | G | G | T  |   |   |   |   |   |   |   |   |
| C  | A  | T  | C  | A   | T | C | A | T   | C  | A        | T        | C | A | T  |   |   |   |   |   |   |   |   |
| A  | T  | T  | A  | T   | T | A | T | T   | A  | T        | T        | A | T | T  |   |   |   |   |   |   |   |   |
| A  | A  | G  | A  | A   | G | A | A | G   | A  | A        | G        | A | A | G  |   |   |   |   |   |   |   |   |
| C  | T  | T  | C  | T   | T | C | T | T   | C  | T        | T        | C | T | T  |   |   |   |   |   |   |   |   |
| A  | T  | G  | A  | T   | G | A | T | G   | A  | T        | G        | A | T | G  |   |   |   |   |   |   |   |   |
| A  | A  | T  | A  | A   | T | A | A | T   | A  | A        | T        | A | A | T  |   |   |   |   |   |   |   |   |
| C  | C  | T  | C  | C   | T | C | C | T   | C  | C        | T        | C | C | T  |   |   |   |   |   |   |   |   |
| C  | A  | G  | C  | A   | G | C | A | G   | C  | A        | G        | C | A | G  |   |   |   |   |   |   |   |   |
| C  | G  | T  | C  | G   | T | C | G | T   | C  | G        | T        | C | G | T  |   |   |   |   |   |   |   |   |
| T  | C  | T  | T  | C   | T | T | C | T   | T  | C        | T        | T | C | T  |   |   |   |   |   |   |   |   |
| A  | C  | T  | A  | C   | T | A | C | T   | A  | C        | T        | A | C | T  |   |   |   |   |   |   |   |   |
| G  | T  | T  | G  | T   | T | G | T | T   | G  | T        | T        | G | T | T  |   |   |   |   |   |   |   |   |
|    |    |    |    |     |   |   |   |     |    |          |          |   |   | T  | G | G |   |   |   |   |   |   |
| T  | A  | T  | T  | A   | T | T | A | T   | T  | A        | T        | T | A | T  |   |   |   |   |   |   |   |   |
| 18 |    |    |    | 19  |   |   |   |     |    |          | 3.32E+05 |   |   |    |   |   |   |   |   |   |   |   |
| 18 | 18 |    |    | 19  |   |   |   |     |    |          | 5.98E+06 |   |   |    |   |   |   |   |   |   |   |   |
| 18 | 18 | 18 | 19 |     |   |   |   |     |    | 1.08E+08 |          |   |   |    |   |   |   |   |   |   |   |   |

SUBSTITUTE SHEET (RULE 26)

Figure 38: Oligo and primer design for V $\lambda$  CDR3 libraries

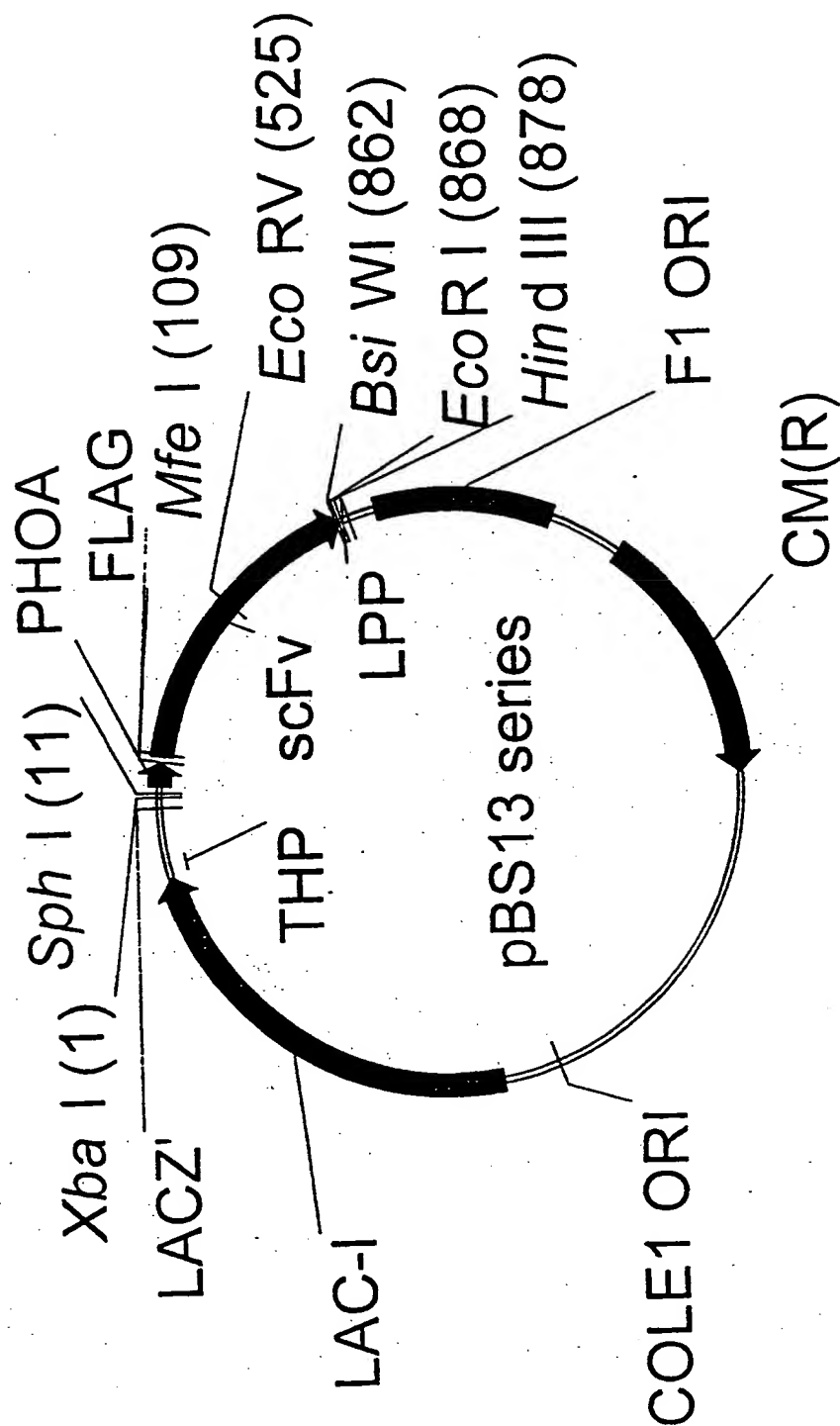


Figure 39: functional map of expression vector series pBS13

Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)

| % soluble | $\kappa 1$ | $\kappa 2$ | $\kappa 3$ | $\kappa 4$ | $\lambda 1$ | $\lambda 2$ | $\lambda 3$ |
|-----------|------------|------------|------------|------------|-------------|-------------|-------------|
| H1A       | 61%        | 58%        | 52%        | 42%        | 90%         | 61%         | 60%         |
| H1B       | 39%        | 48%        | 66%        | 48%        | 47%         | 39%         | 36%         |
| H2        | 47%        | 57%        | 46%        | 49%        | 37%         | 36%         | 45%         |
| H3        | 85%        | 67%        | 76%        | 61%        | 80%         | 71%         | 83%         |
| H4        | 69%        | 52%        | 51%        | 44%        | 45%         | 33%         | 42%         |
| H5        | 49%        | 49%        | 46%        | 67%        | 54%         | 46%         | 47%         |
| H6        | 90%        | 58%        | 54%        | 47%        | 45%         | 50%         | 51%         |

| Total amount<br>compared to H3 $\kappa 2$ | $\kappa 1$ | $\kappa 2$ | $\kappa 3$ | $\kappa 4$ | $\lambda 1$ | $\lambda 2$ | $\lambda 3$ |
|---|------------|------------|------------|------------|-------------|-------------|-------------|
| H1A                                       | 289%       | 94%        | 166%       | 272%       | 20%         | 150%        | 78%         |
| H1B                                       | 219%       | 122%       | 89%        | 139%       | 117%        | 158%        | 101%        |
| H2  | 186%       | 223%       | 208%       | 182%       | 126%        | 60%         | 97%         |
| H3  | 50%        |            | 71%        | 54%        | 59%         | 130%        | 47%         |
| H4  | 37%        | 55%        | 60%        | 77%        | 195%        | 107%        | 251%        |
| H5  | 98%        | 201%       | 167%       | 83%        | 93%         | 128%        | 115%        |
| H6  | 65%        | 117%       | 89%        | 109%       | 299%        | 215%        | 278%        |



Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)

| Soluble amount<br>compared to H3κ2 | κ1   | κ2   | κ3   | κ4   | λ1   | λ2   | λ3   |
|------------------------------------|------|------|------|------|------|------|------|
| H1A                                | 191% | 88%  | 121% | 122% | 26%  | 211% | 76%  |
| H1B                                | 124% | 95%  | 83%  | 107% | 79%  | 142% | 59%  |
| H2                                 | 126% | 204% | 139% | 130% | 66%  | 50%  | 70%  |
| H3                                 | 63%  | -    | 81%  | 49%  | 69%  | 143% | 61%  |
| H4                                 | 40%  | 47%  | 49%  | 54%  | 95%  | 55%  | 125% |
| H5                                 | 69%  | 158% | 116% | 80%  | 72%  | 84%  | 84%  |
| H6                                 | 85%  | 122% | 87%  | 77%  | 162% | 162% | 212% |
|                                    | McPC |      |      |      |      |      |      |
| soluble                            | 38%  |      |      |      |      |      |      |
| %H3κ2 total                        | 117% |      |      |      |      |      |      |
| %H3κ2 soluble                      | 69%  |      |      |      |      |      |      |

## INTERNATIONAL SEARCH REPORT

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| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 6 C12N15/13 C12N15/10 C12N15/62 C12N15/70 C12N1/21<br>C07K1/04 G01N33/53   |  |  |
|--|--|--|
| According to International Patent Classification (IPC) or to both national classification and IPC  |  |  |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 6 C12N C07K G01N   |  |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  |  |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)   |  |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>  |  |  |
| Category *   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.                              |
| A  | EP 0 368 684 A (MEDICAL RES COUNCIL) 16<br>May 1990<br>cited in the application<br>see the whole document<br>---   | 1-55   |
| A  | EUROPEAN J. IMMUNOLOGY,<br>vol. 23, July 1993, VCH<br>VERLAGSGESELLSCHAFT MBH, WEINHEIM, BRD,<br>pages 1456-1461, XP000616572<br>S.C. WILLIAMS AND G. WINTER: "Cloning and<br>sequencing of human immunoglobulin<br>V-lambda gene segments"<br>cited in the application<br>see the whole document<br>---<br>-/-- | 1-55   |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.  |  |  |
| * Special categories of cited documents :<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier document but published on or after the international filing date<br>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>"A" document member of the same patent family |  |  |
| Date of the actual completion of the international search  |  | Date of mailing of the international search report |
| 30 January 1997  |  | 11.02.97   |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016  |  | Authorized officer<br><br>Hornig, H                |

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 96/03647

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
|--|---|-----------------------|
| Category *   | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
| A  | <p>PROC. NATL.ACAD SCI.,<br/>vol. 89, May 1992, NATL. ACAD<br/>SCI.,WASHINGTON,DC,US;,<br/>pages 4457-4461, XP002024223<br/>C. F. BARBAS III ET AL.: "Semisynthetic<br/>combinatorial antibody libraries: a<br/>chemical solution to the diversity<br/>problem"<br/>cited in the application<br/>see the whole document<br/>---</p> | 1-55                  |
| A  | <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF<br/>SCIENCES OF USA,<br/>vol. 89, no. 21, 1 November 1992,<br/>pages 10026-10030, XP000322464<br/>COLLET T A ET AL: "A BINARY PLASMID<br/>SYSTEM FOR SHUFFLING COMBINATORIAL<br/>ANTIBODY LIBRARIES"<br/>see the whole document<br/>---</p>   | 1-55                  |
| A  | <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF<br/>SCIENCES OF USA,<br/>vol. 89, no. 8, 15 April 1992,<br/>pages 3576-3580, XP000384398<br/>GRAM H ET AL: "IN VITRO SELECTION AND<br/>AFFINITY MATURATION OF ANTIBODIES FROM A<br/>NAIVE COMBINATORIAL IMMUNOGLOBULIN<br/>LIBRARY"<br/>see the whole document<br/>---</p>                | 1-55                  |
| A  | <p>PROTEIN ENGINEERING,<br/>vol. 8, no. 1, 1 January 1995,<br/>pages 81-89, XP000500393<br/>KNAPPIK A ET AL: "ENGINEERED TURNS OF<br/>RECOMBINANT ANTIBODY IMPROVE ITS IN VIVO<br/>FOLDING"<br/>cited in the application<br/>see the whole document<br/>---</p>   | 1-55                  |
| A  | <p>ANNUAL REVIEW OF IMMUNOLOGY,<br/>vol. 12, 1 January 1994,<br/>pages 433-455, XP000564245<br/>WINTER G ET AL: "MAKING ANTIBODIES BY<br/>PHAGE DISPLAY TECHNOLOGY"<br/>cited in the application<br/>see the whole document<br/>---</p>   | 1-55                  |
| A  | <p>JOURNAL OF MOLECULAR BIOLOGY,<br/>vol. 224, no. 2, 1 January 1992,<br/>pages 487-499, XP000564649<br/>FOOTE J ET AL: "ANTIBODY FRAMEWORK<br/>RESIDUES AFFECTING THE CONFORMATION OF THE<br/>HYPERCARIABLE LOOPS"<br/>cited in the application<br/>see the whole document<br/>---</p>   | 1-55                  |
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## INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/EP 96/03647

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| A          | <p>NUCLEIC ACIDS RESEARCH,<br/>vol. 21, no. 9, 11 May 1993,<br/>page 2265/2266 XP000575849<br/>WATERHOUSE P ET AL: "COMBINATORIAL<br/>INFECTION AND IN VIVO RECOMBINATION: A<br/>STRATEGY FOR MAKING LARGE PHAGE ANTIBODY<br/>REPERTOIRES"<br/>see the whole document<br/>---</p>   | 1-55                  |
| A          | <p>WO 95 11998 A (UNITED BIOMEDICAL INC) 4<br/>May 1995<br/>see the whole document<br/>---</p>  | 1-55                  |
| A          | <p>ANNALES DE BIOLOGIE CLINIQUE,<br/>vol. 49, no. 4, April 1991, PARIS, FR,<br/>pages 231-242, XP000407361<br/>R.H. MELOEN ET AL.: "The use of peptides<br/>to reconstruct conformational<br/>determinants"<br/>see page 231, right-hand column, paragraph<br/>2 - page 233, right-hand column, line 4<br/>---</p>  | 1-55                  |
| A          | <p>CHEMICAL ABSTRACTS, vol. 122, no. 3,<br/>16 January 1995<br/>Columbus, Ohio, US;<br/>abstract no. 24865z,<br/>COX, JONATHAN P. L. ET AL: "A directory<br/>of human germ-line V.kappa. segments<br/>reveals a strong bias in their usage"<br/>page 227; column 1;<br/>XP002024224<br/>cited in the application<br/>see abstract<br/>&amp; EUR. J. IMMUNOL. (1994), 24(4), 827-36<br/>CODEN: EJIMAF;ISSN: 0014-2980,<br/>1994,<br/>-----</p> | 1-55                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP 96/03647

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| EP-A-0368684                              | 16-05-90            | AU-B- 634186               | 18-02-93            |
|   |                     | AU-A- 4520189              | 28-05-90            |
|   |                     | CA-A- 2002868              | 11-05-90            |
|   |                     | DE-D- 68913658             | 14-04-94            |
|   |                     | DE-T- 68913658             | 08-09-94            |
|   |                     | ES-T- 2052027              | 01-07-94            |
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|   |                     | JP-T- 3502801              | 27-06-91            |
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|   |                     | EP-A- 0725838              | 14-08-96            |
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